The psychometric properties and application of the FRAIL scale and Fried frailty phenotype questionnaire in Japanese community/dwelling older adults

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Doctoral Thesis

The psychometric properties and application of the FRAIL scale and Fried frailty phenotype questionnaire in Japanese community-dwelling older adults

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Summary

Background and purposes of the doctoral thesis

Population aging is accelerating worldwide, from 962 million people older than 65 years in 2017 to an estimated 2 billion people by 2050, which put forward the concept of frailty, become one of the hot issues in geriatrics now. Frailty is defined as a medical syndrome characterized by diminished strength, endurance, and reduced physiologic function and increases an individual's risk of increased dependency and/or death. The associations between frailty and increased risk of adverse outcomes such as mortality and hospitalization have been clearly demonstrated. The prevalence of frailty was ranged from 4.0% to 59.1% and the substantial variation in reported prevalence might be explained by the operational definitions for frailty and the inclusion or exclusion criteria varied between researches. At present, lots of frailty instruments based on different purposes and models have been developed to identify frailty status in older adults. Despite the reliability and validity of several instruments such as the Fried frailty phenotype (FFP) and frailty index (FI) have been well-validated, many of them still have not been robustly validated in the literature, and their prognostic ability was rarely

determined. A two-step approach combines a simple self-reported instrument such as the FRAIL scale and a more extensive examination such as FFP together might be an effective way to tackle frailty because both of them based on the same frailty model and have a solid foundation of the biological theoretical basis. The FRAIL scale is performed first in a large-scale setting to screen frailty and followed by the FFP to assess the real condition of an older adult. However, the FRAIL scale has not been validated in Japan for now. Therefore, the primary purposes of this doctoral thesis were 1) to develop a Japanese FRAIL scale (FRAIL-J) and a modified version based on the FRAIL-J named the Fried Frailty Phenotype Questionnaire (FFPQ) and evaluate the reliability and validity of both questionnaires, and 2) tried to explore an effective application of both questionnaires in Japanese community-dwelling older adults.

Study 1: Reliability and validity of the Japanese FRAIL scale and a modified version in Japanese community-dwelling older adults

The aim of this study was to develop a FRAIL-J and an FFPQ and evaluate the reliability and validity of both questionnaires in Japanese community-dwelling older adults. Participants of this study were from the baseline survey of the Itoshima Frail Study. A total of 858 older adults aged 65-75 years with available data were included. The FRAIL-J comprises 5 existing items comparable to those in the original FRAIL

scale but with broader utilization in the Japanese health care system. In the FFPQ, resistance, ambulation, and loss of weight were the same as those in the FRAIL-J. Fatigue was the same as exhaustion in the FFP and inactivity was assessed using a yes/no question. The FRAIL-J and FFPQ showed low internal consistency (Kuder-Richardson formula 20 coefficients=0.32 and 0.29) and good test-retest reliability (intraclass correlation coefficients=0.79 and 0.72). The correlations ranged from −0.22 to 0.49 when correlating each item with cross-sectional outcomes. Using FFP as a criterion, the area under the curve for the FRAIL-J and FFPQ were 0.86 and 0.88, respectively. The optimal cut-off for FRAIL-J was 2, with a higher Youden index (66.7% vs 20.3% for 3) and a high negative predictive value (NPV=99.5%) but a low positive predictive value (PPV=13.1%). As for the FFPQ, either 2 or 3 were evaluated as cut-off because the Youden index (62.2% vs 58.5%) and NPV (99.7% vs 99.2%) were similar although the PPV was low (9.7% vs 33.3%). Using a 2-point cut-off, both questionnaires had a slight agreement with the FFP. The highest agreement (kappa=0.42) was found between FFP and FFPQ using a 3-point cut-off. Accordingly, The FFPQ and FRAIL-J can be used for frailty screening in Japanese community-dwelling older adults.

Study 2: Associations of objectively measured physical activity and sedentary behavior with frailty status screened by the Japanese FRAIL scale and Fried Frailty Phenotype Questionnaire in Japanese community-dwelling older adults

This study was conducted to examine the association between objectively measured patterns of sedentary behavior (SB) and physical activity (PA) and frailty status defined by the FRAIL-J and FFPQ in Japanese community-dwelling older adults. Data from 65-75 years older adults from the baseline of Itoshima Frail Study were used in the present study. Frailty assessment was performed using the FRAIL-J and FFPQ. SB and PA were measured with an accelerometer. Multinomial logistic regression and receiver operating characteristic curve analyses were used to investigate the associations between SB, PA patterns and frailty status. Of the total 819 older adults, half were male (48.2%). The prevalence of robust, pre-frailty defined by the FRAIL-J and FFPQ were 60.2% vs 50.0%, 27.8% vs 33.3%, and 12.0% vs 16.7%, respectively. Total sedentary time, sedentary time in bouts of ≥ 10 min and ≥ 30 min, and mean sedentary bout duration was not associated with pre-frailty or frailty defined by both questionnaires. On another hand, PA variables including light physical activity (LPA) and moderate-to-vigorous physical activity (MVPA) in bouts of < 10 min (sporadic MVPA) were not associated with pre-frailty or frailty defined by both questionnaires, while total MVPA

time and steps were significantly associated with lower prevalence of frailty. In addition, MVPA in bouts of ≥ 10 min (bouted MVPA) was significantly associated with lower prevalence of frailty defined by the FRAIL-J. Moreover, the 43.25 or 51.63 min/day of total MVPA, 9.13 min/day of bouted MVPA, and 3841 or 3702 steps/day of daily step were suggested as the optimal cut-off value to discriminate between frailty and non-frailty for the FRAIL-J and FFPQ, respectively. Our findings demonstrate a strong relationship between higher levels of total MVPA time, steps and frailty screened by the FRAIL-J and FFPQ. Lower amounts of bouted MVPA or steps may be achievable initial targets in older adults for frailty management. This evidence might inform the future of feasible approaches to managing frailty in Japanese community-dwelling older adults.

Study 3: Using the Fried Frailty Phenotype Questionnaire to assess the effects of an exercise intervention on frailty status in Japanese community-dwelling older adults

The aim of this study was to evaluate whether the FFPQ could be used as an instrument to assess the effect of an exercise intervention on frailty in Japanese community-dwelling older adults. This was a single-group, pre-test, post-test design study. Participants were recruited from the baseline survey of the IFS and a total of 88 with invalid data were included in the final analysis. A set of a multicomponent exercise

intervention program included warm-up, resistance, balance, stretching, and deep breathing exercises (60 minutes, 1 day per week, 6 months) were developed by substantially experienced instructors. In addition, 10-min exercise homework was also asked to be done every day. The exercise intervention was very effective in lowering the frailty score of the FFP and FFPQ. The difference value (95% confidence intervals, 95% CI) of the pre- and post-intervention was -0.68 (-0.83, -0.54) and -0.73 (-0.95, -0.51), respectively. A fair agreement (kappa=0.35) of the intervention effect was found between the two instruments. The item of exhaustion, weakness, slowness, and low physical activity in the FFP and the item of fatigue, resistance, and inactivity in the FFPQ could use to assess the effect of intervention since the change of each item showed the highest correlation with the changes of its corresponding measurements. No significant correlations were found between the change of shrinking in the FFP and ambulation and loss of weight in the FFPQ and the changes of its corresponding measurements. In conclusion, the FFPQ could be used as a rapid instrument to assess the effect of an exercise intervention on frailty in Japanese community-dwelling older adults.

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List of papers

This doctoral thesis consists of the following original publications:

Chen S., Chen T., Kishimoto H., Susaki Y., and Kumagai S. Development of a Fried frailty phenotype questionnaire (FFPQ) for use in screening community-dwelling older adults. *Journal of the American Medical Directors Association*, 2020 Feb; 21(2):272-276.e1.

Chen S., Chen T., Kishimoto H., Yatsugi H., and Kumagai S. Associations of objectively measured patterns of physical activity and sedentary behavior with frailty status screened by the FRAIL scale in Japanese community dwelling older adults. *Journal of Sports Science and Medicine*, 2020 Mar; 19: 166-174.

Abbreviations

95% CI: 95% Confidence Interval

ASMM: Appendicular Skeletal Muscle Mass

AUC: Area Under the Curve

BMI: Body Mass Index

DTA: Diagnostic Test Accuracy

EEPA: Energy Expenditure of Physical Activity

EFS: Edmonton Frailty Scale

FFP: Fried Frailty Phenotype

FFPQ: Fried Frailty Phenotype Questionnaire

FI: Frailty Index

FRAIL: Fatigue, Resistance, Ambulation, Illness, Loss of Weight scale

FRAIL-J: Japanese FRAIL scale

GFI: Groningen Frailty Indicator

GFST: Gérontopôle Frailty Screening Tool

IADL: Instrumental Activities of Daily Living

ICCs: Intraclass Correlation Coefficients

IFS: Itoshima Frail Study

K6: Kessler 6 psychological distress scale

KCL: Kihon Check-List

KR-20: Kuder-Richardson formula 20

LPA: Light Physical Activity

METs: Metabolic Equivalents

MoCA: Montreal Cognitive Assessment

MVPA: Moderate-Vigorous Physical Activity

NHANES: National Health and Nutritional Examination Survey

NPV: Negative Predictive Value

PA: Physical Activity

ROC: Receiver Operating characteristic Curve

PPV: Positive Predictive Value

PRISMA-7: Program of Research on Integration of Services for the Maintenance of Autonomy 7

PSQI: Pittsburgh Sleep Quality Index

SB: Sedentary Behavior

SD: Standard Deviation

SHARE-FI: Frailty Instrument from Survey of Health, Aging and Retirement in Europe

SGS: Sasaguri Genkimon Study

SOF: Study of Osteoporotic Fractures Index

SMMI: Skeletal Muscle Mass Index

TFI: Tilburg Frailty Indicator

TST: Total Sedentary Time

TUGT: Timed Up-and-Go Test

VES: Vulnerable Elders Survey

VIF: Variance Inflation Factor

WHO: World Health Organization

Chapter 1. Background and purpose of the doctoral thesis

1. Background

Population aging is accelerating worldwide, from 962 million people older than 65 years in 2017 to an estimated 2 billion people by 2050, which has profound implications for the planning and delivery of health and social care (World Population Prospects, 2017). The aging population promotes the related research of aging and chronic diseases, put forward the concept of frailty, which has now become one of the hot issues in geriatrics. Frailty is the most problematic expression of population aging. It is a state of vulnerability to poor resolution of homeostasis after a stressor event, which may explain by the consequence of the cumulative decline in many physiological systems throughout a lifetime. This cumulative decline depletes homoeostatic reserves until minor stressor events trigger disproportionate changes in health status (Walston et al., 2006). Figure 1 shows the state of vulnerability diagrammatically: an apparently small insult (e.g. a new drug, minor infection, or minor surgery) results in a striking and disproportionate change in health state (e.g. from independent to dependent) (Clegg et al., 2013). Recently, the associations between frailty and increased risk of adverse outcomes such as all-cause mortality (Chang and Lin, 2015), hospitalization (Kojima, 2016), future falls (Kojima, 2015), disability (Vermeiren et al., 2016), cognitive function (Kojima et

al., 2016), and onset of cardiovascular disease (Veronese et al., 2017) have been clearly demonstrated.

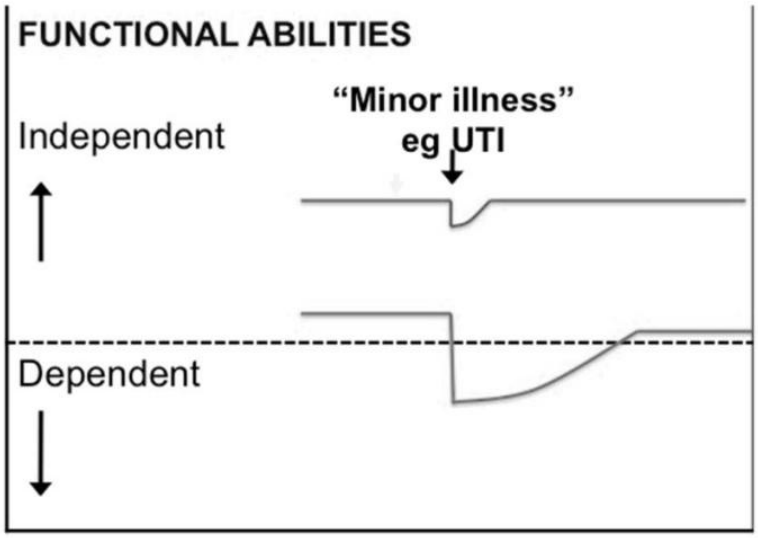

Figure 1. Vulnerability of older adults with frailty to a sudden change in health status after a minor illness (Clegg et al., 2013)

A previous study reviewed the prevalence of frailty (Collard et al., 2012). Of the total 21 community-based cohort studies of 61,500 elderly people, the prevalence of frailty was ranged from 4.0% to 59.1%. The operational definitions for frailty and the inclusion or exclusion criteria varied between these studies might be explained the substantial variation in reported prevalence of frailty. At present, three major models exist to define frailty: frailty phenotype model; deficit accumulation model; and mixed physical and psychosocial model (Dent et al., 2017). Despite many kinds of instruments based on the above three models were developed to detect frailty, it is notable that the

agreement between different frailty instruments is still very low. Recently, Aguayo et al. (Aguayo et al., 2017) examined the agreement between different frailty instruments in a same sample and found that various frailty instruments identified different individuals as frailty and marked heterogeneity also existed in the degree of frailty. In other words, different frailty instruments are based on different concepts, and most pairs cannot be assumed to be interchangeable. Therefore, when choosing a frailty assessment to use, it is essential to select one, which not only accurately identifies frailty and predicts adverse outcomes, but is also simple to use, well-validated, and accounts for the priorities, resources, and objectives of a specific population. This chapter summarized the reliability, validity, target population, strength and limitation of various frailty instruments that were developed to assess frailty.

2. Frailty Phenotype model

2-1 Fried Frailty Phenotype (FFP or Cardiovascular Health Study index)

In 2001, Fried et al. (Fried et al., 2001), through 5000 older adults aged 65 years or older from Cardiovascular Health Study, first proposed the definition of frailty using five major manifestation, defining the condition as the presence of three or more of: (1) unintentional weight loss (10 lbs in past year); (2) self-reported exhaustion; (3)

weakness (grip strength); (4) slow walking speed; and (5) low physical activity. The phenotypic score has a solid foundation of biological theoretical basis (Fried et al., 2001, Xue et al., 2008) and has been most widely used in multiple epidemiological settings to confirm its predictive validity of adverse outcomes (Avila-Funes et al., 2009, Avila-Funes et al., 2008, Chang and Lin, 2015, Makizako, 2017, Mossello et al., 2016, vermeulen, 2011). It is notable that the FFP often has been modified, and these modifications have an important impact on its classification and predictive ability (Theou et al., 2015). Despite its widespread use, the changes of the five indicators cannot provide direct information for their etiology and require a specialized person to measure. Therefore, it is difficult to self-evaluation and uses for screening frailty in a large-scale epidemiological setting. Another major factor inhibiting the application of the FFP is that it excludes some diseases such as Parkinson, Alzheimer's, stroke, depression.

2-2 Fatigue, Resistance, Ambulation, Illness, Loss of Weight (FRAIL) scale

The FRAIL scale was proposed by the International Association of Nutrition and Ageing in 2008 and considered a suitable instrument for screening older adults with frailty (Abellan van Kan et al., 2008). The FRAIL scale is comprised of five components: fatigue, resistance, ambulation, illness, and loss of weight. The total score

ranges from 0–5 (i.e., 1 point for each component; 0=best to 5=worst), and a score of 0 represents participants as robust, 1 to 2 as pre-frail, and 3 to 5 as frail. In contrast with the FFP, the FRAIL scale is brief, cost-effective, and easy to score and interpret, which makes it feasible to perform by telephone at frequent intervals in a large-scale epidemiological setting (Morley et al., 2012). Moreover, it is notable that the FRAIL scale is comparable to more complex measurements such as the FFP and frailty index in predicting mortality and disability (Malmstrom et al., 2014, Ravindrarajah et al., 2013). Until 2010, the FRAIL scale has first been validated in older men in Australia (Hyde et al., 2010). Since then, it has been gradually verified by many countries includes the United States (Morley et al., 2012), China (Dong et al., 2018, Woo et al., 2012), Brazil (Aprahamian et al., 2017a), Korea (Jung et al., 2016), Mexico (Diaz de Leon Gonzalez et al., 2016, Rosas-Carrasco et al., 2016), and European countries (Theou et al., 2013a). Although the FRAIL scale is also known as the rapid screening tool for physical frailty (Dent et al., 2017), the controversy regarding the item of illness still surrounded it. There is broad consensus has been reached that frailty is not synonymous with either comorbidity or disability, the inclusion of the illness category in the FRAIL scale may threaten its face validity as a physical frailty screening instrument. Besides, the type or severity of disease was not exactly defined. Although Morley et al. (Morley et al., 2012)

made a definition of illness and it was used in many studies, there were still some studies using different kinds of diseases (Hyde et al., 2010, Susanto et al., 2018, Theou et al., 2013a). Last, as professional and structural deficiencies in the health care system in the developing nations which also face the aging, it is not easy for older adults to know whether they have had several diseases will also limit its part feasibility.

2-3 Study of Osteoporotic Fractures (SOF) Index

In 2007, Ensurd et al. (Ensrud et al., 2007) according to the study of elderly women with osteoporotic fracture proposed a more simple frailty instrument, the SOF index. The SOF index is comprised of three components: (1) 5% body weight loss in the last year; (2) do you feel full of energy; (3) inability to perform a chair rise five times and frailty is classified as the presence of ≥ 2 components. Similar to the FFP, the SOF index also has an underlying biological causative theory and the predictive validity of the SOF index such as falls, disability, fractures, and mortality has been observed in community-dwelling older adults (Bilotta et al., 2012, Ensrud et al., 2009) and medical inpatients (Forti et al., 2014). Moreover, the SOF is more simple, easy to operate and suitable for population screening and clinical assessment. However, just like the FFP, the SOF index also requires objective measure and patients with an acute medical

condition often cannot perform a five times chair rise. Therefore, SOF does not apply to patients hospitalized for an acute illness or to large-scale epidemiological settings.

2-4 Program of Research on Integration of Services for the Maintenance of Autonomy 7 (PRISMA-7)

The PRISMA-7 is primly designed to screen older adults for potential disability (Raiche et al., 2008). It contains 7 simple self-reported components to identify frailty: (1) older than 85 years; (2) male; (3) health problems which limit activities; (4) support of another person needed; (5) health problems requiring staying at home; (6) social support; (7) use of a cane or walker or wheelchair. Older adults with a total score of more than 3 points are classified as frailty. A recent study investigated the diagnostic test accuracy (DTA) of seven simple instruments for identifying frailty in community-dwelling older adults. The results showed that PRISMA-7 had high sensitivity (83%) for identifying frailty (Clegg et al., 2015). Moreover, the PRISMA-7 shows high-level accuracy (area under the curve, AUC) in identifying frailty and suggested a 4-point score as the cut-off value with high sensitivity (81.5%) and specificity (88.2%) for frailty in community-dwelling older adults (Yaman and Unal, 2018). In addition to the community-dwelling setting, the DTA of PRISMA-7 is also well examined in primary care (Hoogendijk et al., 2013, Sutorius et al., 2016) and the emergency department (O'Caoimh and Costello,

2019). Compare to other frailty instruments, screening for frailty in the primary care and emergency department with the PRISMA-7, is reliable and accurate. However, the limited specificity in previous studies implies many false-positive results which means that it cannot be used as accurate single tests to screen frailty in large-scale epidemiological settings. Moreover, the PRISMA-7 has a tendency to over-screen for frailty thereby limiting its ability as a screening tool (Clegg et al., 2015). In addition, almost a decade past after the PRISMA-7 has been developed, almost all studies focused on the DTA of the PRISMA-7, it still has previously less evidence regarding the predictive validity for adverse outcomes. It should be noted that the PRISMA-7 also includes the item on disability to measure frailty. Although frailty, disability, and comorbidity are inter-related, there are distinct clinical entities.

2-5 Gérontopôle Frailty Screening Tool (GFST)

The GFST is designed as a tool for assisting general practitioners in detecting non-disabled frail older adults among community-dwelling elderly ≥ 65 years old with basic activities of daily living. It comprises two steps: a questionnaire is performed first and followed by a general practitioner's judgment of frailty status (Demougeot et al., 2013, Vellas et al., 2013). The questionnaire includes 6 components: (1) living alone; (2) weight loss in the last 3 months; (3) feeling tired in the last 3 months; (4) feeling

difficulty to move in the last 3 months; (5) memory complaints; (6) slow gait speed. Frailty status should be considered if got 3 or more “Yes”. The GFST combines simple questionnaire and general practitioner’s judgment together seems a good way to tackle frailty, however, one main factor which limited its applicability. Despite the GFST highlights the importance of the general practitioner's clinical impression on the frailty diagnosis process, the only clinical impressions may not be sufficient to identify frailty (Fougere et al., 2017). Moreover, it does not give any specific guidance for the general practitioners about how to identify frailty, and its reliability and predictive ability studies have not yet been established.

2-6 Frailty Instrument from Survey of Health, Aging, and Retirement in Europe (SHARE-FI)

The SHARE-FI is developed as a simple instrument for screening frailty approximating based on the FFP definition in aged 50 years and older Europeans (Romero-Ortuno et al., 2010). Just like FFP, the SHARE-FI also has five domains (weight loss, low physical activity, exhaustion, slowness, and weakness) comprising four questions and one measurement: (1) have you not been able to do what you want in the past month due to poor mental state; (2) do you have anorexia or eat less than before; (3) compared with 3 months ago, in the past month is it difficult for you to walk 100

meters or climb staircase; (4) how often do you perform light-to-moderate physical activity such as pruning flowers, cleaning the car or taking a walk; (5) grip strength. Older adults are considered frail if they meet three or more of these criteria and the classification into frailty categories are automatic. A subtype of the SHARE-FI named SHARE-FI75+, which aims to screen older adults with frailty particularly in aged 75 years or more (Romero-Ortuno and Soraghan, 2014). The predictive validity of the SHARE-FI such as mortality and incident disability has been well-validated in community settings (Romero-Ortuno, 2011, Romero-Ortuno et al., 2011, Romero-Ortuno et al., 2010, Theou et al., 2013a). In addition, the convergent and discriminate validity also has been validated in a recent study (McDonagh et al., 2019). Not only in community-dwelling older adults, the SHARE-FI also showed good validity in other different settings (Alonso Salinas et al., 2016, Alonso Salinas et al., 2018, Alonso Salinas et al., 2017, Zhang et al., 2019), however, only has limited predictive ability in the emergency department (Fallon et al., 2018). Indeed, the SHARE-FI is intended to facilitate the rapid frailty instrument rather than replicating FFP in the European community level. A recent study also has shown the SHARE-FI is similar in effectiveness to FFP in screening frailty and predictive mortality in community-dwelling older adults, while the SHARE-FI is considered more specific and easily

manipulated than FPP (Romero-Ortuno, 2013). Compare to FFP, it uses a question to assess slowness instead of gait speed but remains grip strength measurement. Despite the objective measurement maybe make the SHARE-FI more effective in predicting adverse outcomes, it also limited the ability in a large-scale epidemiological setting.

2-7 Objective measurements

A recent systematic review investigated the DTA of simple frailty instruments compare to FFP in community-dwelling older adults (Clegg et al., 2015). The results showed that gait speed and timed up-and-go test have high sensitivity for identifying frailty. However, limited specificity implies many false-positive results make these objective measurements cannot be used as accurate single tests to identify frailty. Moreover, objective measurements cannot be used to reliably identify pre-frail status among older adults.

2-7-1 Gait speed

Gait speed is very valuable for the identification of frailty. It can also replace the complex assessment and enables the elderly to self-test and monitor frailty (Schoon et al., 2014). A recent study comparing the relationship between each of the five items of FFP found that gait speed is the most relevant to frailty (Abizanda et al., 2012, Hoogendijk et al., 2015). Using the value of 0.8 m/s as the cut-off is the optimal to

diagnosis frailty in the primary care setting according to the likelihood ratios of the probability of frailty in patients with and without slow walking speed (Castell et al., 2013).

2-7-2 Grip strength

Grip strength is widely used and it is also an important measurement in FFP and sarcopenia among older adults. Greene et al. (Greene et al., 2014) reported that based on the results of the comprehensive assessment of older adults, according to the frailty defined by the phenotype, the accuracy of using grip strength to distinguish between frailty and non-frailty was less than the timed up-and-go test. However, after the distinction of gender, the accuracy rate reached 77.65%, exceeding the timed up-and-go test. In general, the value of grip strength for frailty is slightly lower than gait speed but also has strong practicality.

2-7-3 Timed Up-and-Go Test (TUGT)

TUGT is generally used to comprehensively reflect the balance of older adults. Previous studies also found that older adults with frailty have a longer time for the TUGT (Chang et al., 2011, Davis et al., 2011). Recent studies found that TUGT (cutoff: 10 s) is a sensitive and specific objective measure can effectively identify the frailty

where the full application of FFP is impracticable in older adults (Abizanda et al., 2012, Gobbens and van Assen, 2012, Greene et al., 2014, Savva et al., 2013).

3. The deficit accumulation model

The deficit accumulation model is also known as Frailty Index (FI). The FI was firstly proposed by Rockwood and Mitnitski (Mitnitski et al., 2001) as a way to incorporate the multidimensional nature of frailty into an operational definition. 92 baseline variables of abnormal laboratory values, disease states, disabilities, symptoms, and signs are used to identify frailty. The frailty index is a simple calculation of the presence or absence of each variable as a proportion of the total. For example, an older adult who has 20 deficits present of a possible 92, then the frailty index can be calculated (20 / 92 = 0.22). The cut-off value to define frailty status is suggested by more than 0.25. Rockwood also points out that when FI is 0.67, the human system will be at the critical point of the collapse, even minor stressor events trigger death (Rockwood and Mitnitski, 2006). The FI is one of the two most widely used frailty instruments and it also often has been modified. From the original 92-item to more easier versions (at least 30 items) such as 30-item (Dallmeier et al., 2019), 40-item (Romero-Ortuno and Kenny, 2012, Searle et al., 2008, Song et al., 2010), 46-item

(Blodgett et al., 2015b), 57-item (Wallace et al., 2015) , and 70-item (Theou et al., 2013b). In contrast with the FFP that modifications of the FFP may impact its classification and predictive ability, the modifications of the FI seem less impact on classification and predictive ability no matter among the community-dwelling older adults or patients. To date, the FI is well-validated and has been applied to multiple settings worldwide. There is a growing body of studies found the FI has a higher predictive ability of adverse clinical events than other frailty instruments in both hospital and community settings (Dent and Perez-Zepeda, 2015, Theou et al., 2013a). Despite this method are easy to understand and has better predictive ability, the FI usually needs to investigate some information derived from the comprehensive geriatric assessment. Therefore, it is difficult to self-evaluate and use for screening frailty in a large-scale epidemiological setting.

4. Mixed physical and psychosocial model

4-1 Tilburg Frailty Indicator (TFI)

The TFI is a self-administered questionnaire developed by Gobbens et al. (Gobbens et al., 2010) based on the conceptual framework of frailty for self-assessment of the debilitating condition of the elderly in the community in the Netherlands during 2010. It

covers 3 aspects contains 15 simple self-reported items: physical components (health, weight loss, difficulty in walking, balance, hearing, vision, gripping and tiredness); psychological factors (memory, feeling down, anxiety and coping); and social elements (living alone, social isolation, social support). Older adults with more than five items are identified as frailty based on a large sample size study (van Assen et al., 2016). A recent systematic review summarized 38 frailty instruments and found that the TFI was the most extensively examined in terms of psychometric properties including face and content validity, internal consistency and test-retest reliability, construct validity (ie, convergent and divergent validity), and predictive validity (Sutton et al., 2016). The TFI is widely used in frailty screening in the community-dwelling older adults in the Netherland. In addition to the Netherland, the TFI is also validated in Brazil (Santiago et al., 2013), Italy (Mulasso et al., 2016), Span (Vrotsou et al., 2018), Turkey (Topcu et al., 2019), Germany (Freitag et al., 2016), Poland (Uchmanowicz et al., 2016), and China (Dong et al., 2017). Although the psychometric properties of the TFI have been extensively examined using in community-dwelling older adults, more studies on the properties in other samples (e.g. hospitalized older adults or patients in an emergency department) are still required. Moreover, only a few studies have determined the predictive power of the TFI for adverse outcomes such as all-cause death. Also of note

is that the weighting of components of the TFI still needs to be further study (Gobbens et al., 2017).

4-2 Edmonton Frailty Scale (EFS)

The EFS is a simple frailty instrument developed by Rolfson et al. (Rolfson et al., 2006) according to a study that investigated 364 older adults aged 65 years or older. It contains nine components including cognition, nutrition, continence, functional independence, functional performance, general health status, mood, polypharmacy, and social support. A score of 0-5 is considered to be robust, 6-7 is apparently vulnerable, 8-9 is mildly frail, 10-11 is moderately frail, and ≥ 12 is severely frailty. The EFS is considered as a valid and reliable instrument for assessing frailty in primary and acute care and hospitalized older adults (Amabili et al., 2019, Hilmer et al., 2009, Petty et al., 2006). Although the EFS has been validated in other settings, it is notable that the evidence is only from a few studies. Recently, a Chinese version was developed and used to investigate the factors in Chinese urban communities (Yang et al., 2018). Moreover, Fabricio-Wehbe et al. translated the EFS into Portuguese and assessed the cross-cultural adaptation (Fabricio-Wehbe et al., 2009). Further study still needed to examine the validation and cross-culture adaption in other samples and countries. In addition, the reliability and validity of the EFS have not been well-validated.

4-3 Groningen Frailty Indicator (GFI)

The GFI is originally developed by Steverink et al. (Steverink et al., 2001) and used to assess frailty for the home-dwelling and nursing home settings, with moderate scorer reliability and internal consistency widely used in the Netherland. It contains 15 self-reported items in four dimensions including physical factors (9-items), cognitive component (1-item), social factors (3-items), and psychological components (2-items). The GFI score of 0 to 3 is considered to be robust, and ≥ 4 is classified as frailty (Schuurmans et al. 2004). The reliability and validity of the GFI have been well-validated either in the community-dwelling or home-dwelling and institutionalized older adults (Bielderman et al., 2013, Metzelthin et al., 2010, Peters et al., 2015, Peters et al., 2012). Moreover, despite the cross-cultural validation of GFI also has been gradually examined and presented acceptable validity and reliability in a Chinese nursing home residents (Xiang et al., 2019) and German older adults (Braun et al., 2018), the GFI study is mainly confined to the Netherlands and cross-cultural studies are still required in many other countries and settings.

4-4 Vulnerable Elders Survey (VES)

The VES is a self-assessment questionnaire composed of 13 items involves 6 questions on physical function, 5 questions on daily living ability, self-reported health,

and age. VES score ≥ 3 is considered to be frailty (Saliba et al., 2001). The VES as a frailty screening tool, the negative predictive value is of great significance (Castagneto et al., 2013). A study translated the VES into Portuguese and found good test-retest reliability and internal consistency (Carneiro et al., 2015). This instrument is now widely used in older cancer and results showed that the VES can be used to predict whether cancer patients were at risk of toxicity during chemotherapy, but the sensitivity and specificity of these studies were inconsistent (Luciani et al., 2015). Moreover, the validity of the VES in predicting adverse outcomes such as disability, institutionalization, and mortality has been validated in a recent study in community-dwelling elderly. The results showed that despite the VES may predict the occurrence of disability, mortality, and institutionalization, the AUC analysis showed that this instrument did not have the good discriminatory ability. Therefore, more studies regarding the validity and reliability of the VES are still needed in many other countries and settings.

4-5 Kihon Checklist (KCL)

The KCL was originally developed by the Japanese Ministry of Health, Labor and Welfare to evaluate the eligibility of older individuals for services provided by Long-Term Care Insurance containing 25 items regarding the instrumental and social activity

of living, physical functions, nutritional status, oral function, cognitive function, and depressive mood. In 2011, Ogawa et al. firstly assessed the validity of the KCL based on similar principles to the FI and investigated its biomarkers in older adults (Ogawa et al., 2011). To date, the cut-off point of the KCL that how to define frailty status is still inconsistent. Older adults with a score of 3/4 points were indicated as pre-frail, and 7/8 points were indicated as frailty using the FFP as a standard reference (Satake et al., 2016). Other studies suggest that the total KCL score with more than 7 points indicating general frailty (Sampaio et al., 2015, Yamada et al., 2017). A recent study identified five types of frailty defined by the KCL in community-dwelling older adults: the experience of falling, pre-frailty, oral frailty, housebound and severe frailty (Kera et al., 2017). Therefore, further study is still needed to determine the optimal cut-off point to identify frailty status. Recently, the predictive validity of the KCL has been well-validated. A study showed that the predictive ability of the KCL score for physical strength and cognitive function decline in community-dwelling older adults (Fukutomi et al., 2013). Another study found that the classification of frailty status by the KCL (0-3 were classified as robust, 4-7 as pre-frail, and 8 + as frail) could be a significant instrument to predict the incidences of dependency and mortality in older adults (Satake et al., 2019, Satake et al., 2017). Although the original language of the KCL is Japanese

and widely used in Japan, the KCL was already translated into English (Arai and Satake, 2015), Brazilian Portuguese (Sewo Sampaio et al., 2014), Korean (Jang et al., 2017), and Turkish (Esenkaya and Dokuzlar, 2019).

5. Other frailty instruments

Other frailty instruments such as the Easy Care (Craig et al., 2015), Frailty Risk Score (Pijpers et al., 2009), Frailty Trait Scale (Garcia-Garcia et al., 2014), Sherbrooke Postal Questionnaire (Metzelthin et al., 2010), and Clinical Frailty Scale (Rockwood et al., 2005), while not included in this chapter owing to its limited utilization and also have many limitations same as other frailty instruments introduced in the present chapter.

6. Comparison of various frailty models

Presently, no existing frailty instrument is considered to be a gold standard. The absence of consensus on diagnosis frailty resulting in the plethora of instruments currently hampers the implementation of frailty management. Among the existing three major models, the frailty phenotype model mainly focused on physical frailty and the most representative instrument is FFP; the deficit accumulation model is based on the

accumulation of conditions or disabilities, emphasizing the number rather than the nature of deficits; the mixed physical and psychosocial model is also known as the multidimensional model defines frailty as a dynamic state of loss affecting 1 or more domains of function including cognitive, physical, and social areas. Indeed, different frailty models are based on different concepts and should rather be considered as complementary. Aguayo et al. (Aguayo et al., 2017) recently confirmed the point that frailty instruments based on different models identified different individuals as frailty and marked heterogeneity also existed in the degree of frailty. Unfortunately, the three models are often wrongly considered as alternatives or assumed to be interchangeable. Indeed, compare to the deficit accumulation model, the frailty phenotype model and multidimensional model are easier to operate and discriminates broad levels of risk. On the other hand, while the deficit accumulation model requires additional clinical information makes the risk of adverse outcomes to be defined more precisely in contrast to the frailty phenotype model and multidimensional model. Therefore, the combined/sequential use of these models is advisable because they provide distinct and complementary information about the risk profile of older adults. For instance, using the FRAIL scale or TFI as the first step to screening potential frail older adults in a large-scale setting, then using the FI or more extensive examinations such as Comprehensive

Geriatric Assessment or FFP to assess the detailed status of an older adult and provide a corresponding suggestion.

7. The utilization of frailty instruments in Japan

The aging population in Japan is increasing more rapidly than that of any other country in the world. According to the governmental report, by 2060, 40% of the entire population in Japan will be aged 65 years or older (Japan National Institute of Population and Social Security Research, 2012). Therefore, develop effective methods to manage frailty status are urgently required particularly in Japan. Using which model or instrument to define frailty status is the first knotty problem to be deal with. There is a growing body of studies investigating various areas of frailty such as risk factors and the associations with adverse outcomes. No doubt, the most widely used frailty instrument is the FFP. A recent meta-analyses showed that the pooled prevalence of frailty based on FFP in Japan was 7.4% and the age-stratified prevalence was 1.9%, 3.8%, 10.0%, 20.4%, and 35.1% for those aged 65-69, 70-74, 75-79, 80-84, and 85 years and older, respectively (Kojima et al., 2017). In addition to the FFP, two instruments have been developed and used in Japan for identifying vulnerable older adults with high risks of adverse health outcomes, such as long-term care or disability.

One is the KCL which has been introduced in the present chapter, another one is the Kaigo-Yobo Checklist, which is a 15-item questionnaire to identify older adults at high risk of in need of long-term care (Shinkai et al., 2010). Although these two instruments have good accuracy to screen the FFP indicated its potential ability to screen frailty, the main limitation is its concept. The two instruments were originally aimed to screen older adults with the risk of disability or long-term care. However, there is broad consensus has been reached that frailty is not synonymous with disability. Thus, the different theoretical models or constructs of the two instruments limit its ability to screen older adults with the FFP. They are more close to the definition of FI rather than the FFP, however, less previous studies investigate the diagnostic test accuracy of the two instruments with the FI.

8. Purposes of the doctoral thesis

To sum up, there are lots of frailty instruments based on different purposes and models developed to identify frailty in older adults. Despite the reliability and validity of many of these instruments had been validated, there are still have many frailty instruments that had not been robustly validated in the literature, and their prognostic ability was rarely determined. A two-step approach combines a simple self-reported

instrument such as the FRAIL scale or TFI and a more extensive examination such as FFP or FI together might be an effective way to tackle frailty. Among the various frailty instruments, the combination of the FRAIL scale and FFP might be a better one because both of them based on the same model and have a solid foundation of the biological theoretical basis. The FRAIL scale is performed first in a large-scale setting to screen frailty and followed by the FFP to assess the real condition of an adult. However, the FRAIL scale has not been validated in Japan for now. Therefore, the primary purposes of this doctoral thesis were to develop a Japanese FRAIL scale (FRAIL-J) and a modified version based on the FRAIL-J named the Fried Frailty Phenotype Questionnaire (FFPQ) and evaluate the reliability and validity of both questionnaires, and tried to explore an effective application of both questionnaires in Japanese community-dwelling older adults. Accordingly, the present thesis had three objectives. The first objectives were to develop a Japanese FRAIL scale and tried to modify it to make the FRAIL scale more close to the FFP, then to evaluate the reliability and validity of both scales in Japanese community-dwelling older adults (Study 1 in Chapter 2). The second objective was to investigate the association between lifestyle factors, particularly the objectively daily physical activity, and frailty defined by the FRAIL-J and FFPQ in Japanese community-dwelling older adults (Study 2 in Chapter 3). The

third objective was to examine whether the FFPQ can be used to assess the effects of an exercise intervention on frailty status in Japanese community-dwelling older adults (Study 3 in Chapter4).

Table 1. Comparisons of frailty instruments

Instruments	Components	Diagnosis	Reliability	Validity	Limitation
FFP	Shrinking, exhaustion, slowness, weakness, low physical activity, total of 5 score	⩾ 3	None	Predictive validity Concurrent validity	Needs objective measurements and population reference values
FRAIL	Fatigue, resistance, ambulation, illness, loss of weight, total of 5 score	⩾ 3	Test-retest reliability Internal consistency	Predictive validity Concurrent validity	Illness item may threaten the face validity
SOF	Weight loss, exhaustion, unable to rise from chair 5 times, total of 5 score	⩾ 2	None	Predictive validity	Needs objective measurement; cannot screen pre-frailty
PRISMA-7	Age, male, social support, and ADLs, total 7 items, total of 7 score	⩾ 3	Test-retest reliability	Concurrent validity	Including item of disability and has less evidence regarding the predictive validity
GFST	(i)self-report; (ii) clinical judgment	Not clear	None	None	Less evidence regarding the predictive validity
SHARE-FI	Weight loss, low physical activity, exhaustion, slowness, weakness, total of 5 score	⩾ 3	None	Predictive validity Concurrent validity	Needs objective measurement and population reference value
FI	At least 30 items, accumulated health deficits: score of 0 (no deficits) to 1.0 (all deficits)	> 0.25	None	Predictive validity Concurrent validity	Needs information derived from the comprehensive geriatric assessment; cannot screen pre-frailty
TFI	Physical, psychological and social aspects (15 items), total of 15 score	Not clear	Test-retest reliability Internal consistency	Predictive validity Concurrent validity	Less evidence regarding the predictive validity; the weighting of each aspect; missing cut-off value for frailty status
EFS	Cognition, nutrition, continence, functional independence, functional performance, general health status, mood, polypharmacy, and social support, total of 17 score	⩾ 8	None	Concurrent validity	Less evidence regarding the reliability and validity; have more categories (5) of frailty status
GFI	Physical, cognitive, social and psychological aspects (15 items), total of 15 score	⩾ 4	Scorer reliability Internal consistency	Concurrent validity	Less evidence regarding the predictive validity; the weighting of each aspect; cannot screen pre-frailty
VES	Physical function, daily living ability, self-reported health, and age (13 items), total of 13 score	⩾ 3	Test-retest reliability Internal consistency	Predictive validity Concurrent validity	Less evidence regarding the reliability and validity; discriminatory ability not good
KCL	Instrumental and social activity of living, physical and cognitive functions, nutritional status, oral function, and depressive mood (25 items), total of 25 score	Not clear	None	Predictive validity Concurrent validity	Including item of disability; cut-off value for frailty status not consistent

FFP: Fried Frailty Phenotype; FRAIL: Fatigue, Resistance, Ambulation, Illness and Loss of Weight Index; SOF: Study of Osteoporotic Fracture Index; PRISMA-7: Program of Research on Integration of Services for the Maintenance of Autonomy 7; GFST: Gérontopôle Frailty Screening Tool; SHARE-FI: Frailty Instrument from Survey of Health, Aging and Retirement in Europe; FI: Frailty Index; TFI: Tilburg Frailty Index; EFS: Edmonton Frailty Scale; GFI: Groningen Frailty Indicator; VES: Vulnerable Elders Survey; KCL: Kihon Check-list; .

Chapter 2. Reliability and validity of the FRAIL scale and a modified version in Japanese community-dwelling older adults (study 1)

1. Introduction

Physical frailty is defined as a medical syndrome with multiple causes and contributors. It is characterized by diminished strength, endurance, and reduced physiologic function and increases an individual's risk of increased dependency and/or death (Morley et al., 2013). The prevalence of physical frailty in community-dwelling older adults ranges from 4.0% to 17.0% (Collard et al., 2012). The associations between frailty and increased risk of adverse outcomes such as all-cause mortality (Chang and Lin, 2015), hospitalization (Kojima, 2016), future falls (Kojima, 2015), disability (Vermeiren et al., 2016), cognitive function (Kojima et al., 2016), and onset of cardiovascular disease (Veronese et al., 2017) have been clearly demonstrated. As frailty is increasingly recognized, accurate and timely detection of frailty in older adults becomes more urgent and necessary. To date, numerous frailty measurements designed to diagnose the syndrome have been published (Buta et al., 2016, Dent et al., 2016), with the Fried Frailty Phenotype (FFP) (Fried et al., 2001) and Frailty Index (FI) (Mitnitski et al., 2001) being the most widely used. Despite their widespread used, the FFP and FI are not easily implemented in settings such as a busy clinic or large-scale epidemiological study, as the former requires objectively measured and population

reference values and the latter requires information derived from the Comprehensive Geriatric Assessment.

As a simpler alternative, a 5-item FRAIL scale was proposed by the International Association of Nutrition and Aging in 2008 (Abellan van Kan et al., 2008). This scale is a hybrid measure comprising two functional components, two biological components, and one deficit accumulation component. Moreover, it is notable that the FRAIL scale is comparable to more complex measurements such as the FFP and frailty index in predicting mortality and disability (Malmstrom et al., 2014, Ravindrarajah et al., 2013). Until 2010, the FRAIL scale has first been validated in older men in Australia (Hyde et al., 2010). Since then, it has been gradually verified by many countries includes the United States (Morley et al., 2012), China (Dong et al., 2018, Woo et al., 2012), Brazil (Aprahamian et al., 2017a), Korea (Jung et al., 2016), Mexico (Diaz de Leon Gonzalez et al., 2016, Rosas-Carrasco et al., 2016), and European countries (Theou et al., 2013a). However, the FRAIL scale has not been validated in Japan. Recently, previous studies evaluated the criterion validity of the FRAIL scale with the FFP and found moderate to good accuracies at a 2-point cut-off (Aprahamian et al., 2017a, Dong et al., 2018). Moreover, in the Asia-Pacific guidelines for frailty management (Dent et al., 2017), the FRAIL scale is also considered as a rapid screening for the FFP. However, one of the

constituent items in the FRAIL scale, illness, may limit its validity for the FFP screening. First, the FFP does not include a comorbidity category, the inclusion of illness in the FRAIL scale may threaten its face validity. Additionally, replaced physical activity with illness may change the theoretical constructs or models. Thus, according to the FFP and our previous Sasaguri Genkimon Study (SGS) (Chen et al., 2015), we tried to develop a modification, the Fried Frailty Phenotype Questionnaire (FFPQ), specifically focused on the FFP screening in the present study.

Therefore, the purposes of this study were 1) to develop a Japanese FRAIL scale (FRAIL-J) and an FFPQ, and 2) to evaluate the reliability and validity of both questionnaires in Japanese community-dwelling older adults.

2. Methods

2-1 Study participants

The present study was a cross-sectional analysis using the baseline data of the Itoshima Frail Study (IFS) conducted from September to December 2017. The IFS is an ongoing community-based prospective study in Itoshima City (Japan), aiming to explore modifiable lifestyle factors either causing or protecting against frailty in older adults. Of approximately 10,000 elderly residents of Itoshima aged 65 to 75 years who

were not certified as requiring nursing care by the national long-term care insurance system, 5,000 older adults were randomly selected according to the residential area, sex, and age. Study information sheets and questionnaires were mailed to these subjects along with an invitation to visit a community center for further assessments. Of 5,000 individuals we contacted, 1,624 submitted questionnaires and 949 participated in further assessments, for a response rate of 32.6% and 19.0%, respectively. In the present study, individuals who did not participate in any physical tests were excluded. In addition, subjects with missing or invalid data were excluded (Figure 2). This study was approved by the Institutional Review Board of Kyushu University, Japan. All the participants provided written informed consent.

2-2 Frailty screening

2-2-1 Fried Frailty Phenotype (Table 1)

The FFP includes 5 components: shrinking, weakness, exhaustion, slowness, and low physical activity. The total score ranges from 0 to 5, participants scoring 3 to 5, 1 to 2, and 0 are designated frail, pre-frail and robust, respectively. In our previous SGS study, we defined the low physical activity domain of the FFP using a population reference assessed by a tri-axial accelerometer (Chen et al., 2015). In this study, we used the same definition of the FFP as in the SGS.

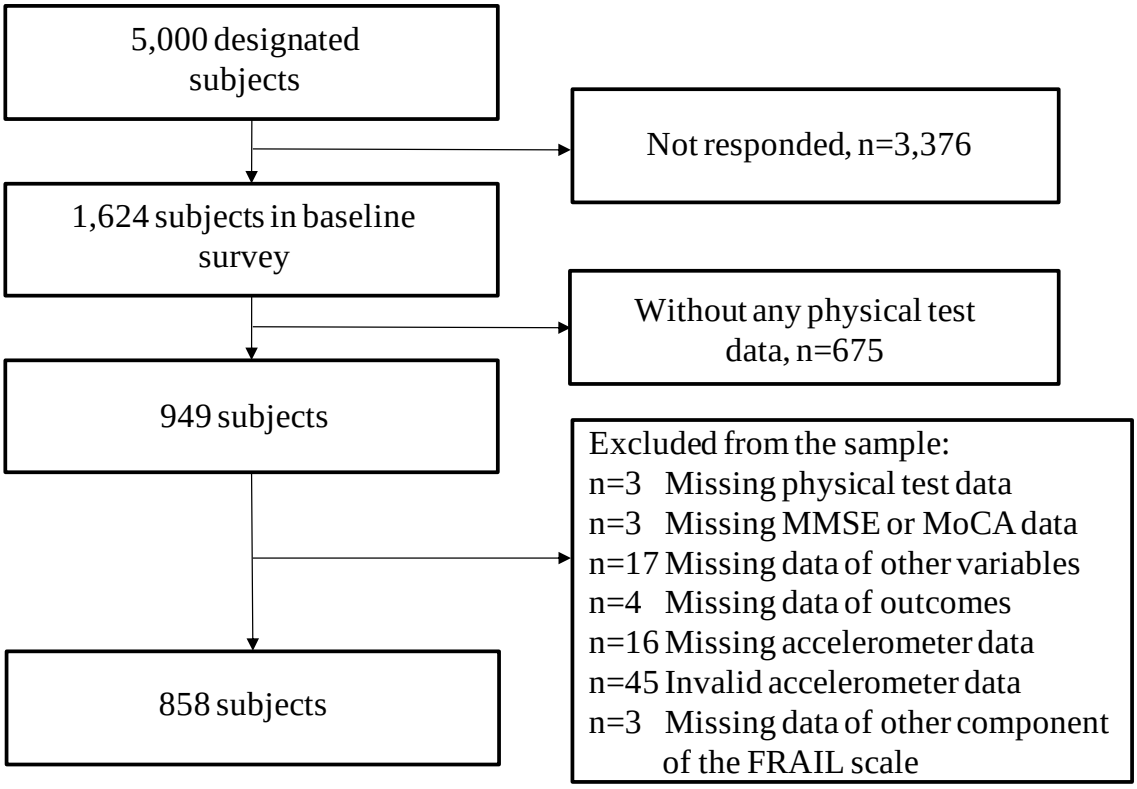

Figure 2. Flow chart of participation

Table 2. Operational definition of the Fried Frailty Phenotype

	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: "Do you feel that everything you do is an effort?", "Do you feel exhausted without any reason? "
Slowness	Time of 5-metre walk test at one's maximum walking speed in the highest 20%, stratified by gender and height (gender-specific cutoff: a medium height).
Male	Time ⩾ 3.56 s for height < 162.0 cm or Time ⩾ 3.21 s for height ⩾ 162.0 cm
Female	Time ⩾ 4.25 s for height < 148.7 cm or Time ⩾ 3.61 s for height ⩾ 148.7 cm
Low physical activity	Lowest 20% of energy expenditure of physical activity by a triaxial 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.

2-2-2 Japanese version of the FRAIL scale (Table 2)

The FRAIL scale includes 5 items and the total score ranges from 0 to 5 points. We modified the original items using comparable existing items that have been more broadly utilized in the Japanese health care system. Cohen's kappa test was used to assess the level of agreement between various preliminary question candidates for fatigue, resistance, ambulation, inactivity, and loss of weight and their corresponding item in the FFP. The highest agreement of each item with the corresponding item was used to determine the final version of FRAIL scale. The contents of the Japanese version of the FRAIL scale are as follows: (1) fatigue was assessed by asking participants if they had felt tired without a reason in the last two weeks; (2) resistance was evaluated by asking participants if they were able to climb stairs without using a handrail or wall for support; (3) ambulation was evaluated by asking participants if they could walk 1 km without resting; (4) illness was defined as the presence of 5 or more of 11 diseases; and (5) loss of weight was defined as unintentional weight loss > 2–3 kg in the previous 6 months. Among the five items, fatigue, resistance, and loss of weight were obtained from the "Kihon Checklist", which was designed by the Japanese Ministry of Health, Labor and Welfare and widely used to identify older adults who are at risk of needing long term care (Arai and Satake, 2015). Ambulation

was obtained from the “Kaigo-Yobo Checklist” which is also a well-validated index for assessing the risk of long term care (Shinkai et al., 2010).

2-2-3 Fried Frailty Phenotype Questionnaire (Table 2)

The items of resistance, ambulation, and loss of weight in the FFPQ were the same as those in the FRAIL-J. Fatigue was the same as the item of exhaustion in the FFP and inactivity was assessed using a simple yes/no question: “Does your sitting or lying time account for 80% or more of your waking time?”. As for the cut-off of inactivity, SGS data showed that older adults with low physical activity spent 70% of their waking time in sedentary behavior. However, 70% may not be a good cut-off for frailty diagnosis. A previous study found that in the older adults who spent approximately 70% of their waking time in sedentary behavior at baseline, the presence and absence of frailty two years later were equal. Moreover, in the same study, a higher percentage of sedentary behavior was associated with a higher risk of frailty (hazard ratio=1.55, per 10% increase) (Song et al., 2015). Therefore, a cut-off of 80% was selected in this study.

Table 3. The definition of FRAILQ-J and FFPQ

	FRAIL-J	FFPQ
Fatigue	In the last 2 weeks have you felt tired without a reason? 1 = Yes, 0 = No.	In the last one month: Do you feel that everything you do is an effort?, Do you feel exhausted without any reason? 1 = Most of the time, 2 = Some of the time, 3 = A little of the time, 4 = None of the time. Either of two questions responses of "1" or "2" are scored as 1 and others as 0.
Resistance	Do you normally climb stairs without using handrail or wall for support? 0 = Yes, 1 = No.	Do you normally climb stairs without using handrail or wall for support? 0 = Yes, 1 = No.
Ambulation	By yourself and not using aids, do you have any difficulty walking 1 km without resting? 1 = Yes, 0 = No.	By yourself and not using aids, do you have any difficulty walking 1 km without resting? 1 = Yes, 0 = No.
Illness/Inactivity	The illnesses include hypertension, diabetes, cancer (other than a minor skin cancer), chronic lung disease, heart attack, congestive heart failure, angina, asthma, arthritis, stroke, and kidney disease. The total illnesses (0–11) are recoded as 0–4 = 0 and 5–11 = 1.	Does your sitting or lying time account for 80% or more of your waking time in a day. 1 = Yes, 0 = No.
Loss of weight	Unintentional weight loss > 2–3 kg in the past 6 months. 1 = Yes, 0 = No.	Unintentional weight loss > 2–3 kg in the past 6 months. 1 = Yes, 0 = No.

FRAIL-J, Japanese FRAIL scale; FFPQ, Fried Frailty Phenotype Questionnaire.

2-3 Cross-sectional outcome measures

Cross-sectional outcomes including (1) body mass index (BMI); (2) grip strength; (3) gait speed, based on a 5-meter walking test at one's maximum and normal walking speed; (4) open-eyed one-leg standing test (max=120sec); (5) physical activity including energy expenditure of physical activity (EEPA) and total sedentary time (TST) were objectively measured using a tri-axial accelerometer (Active style Pro HJA-350IT, Omron, Kyoto, Japan); (6) cognitive function was measured using the Montreal Cognitive Assessment (MoCA); (7) instrumental activity of daily living (IADL) was measured using the Tokyo Metropolitan Institute of Gerontology Index of Competence; (8) fall experience was evaluated with one self-reported question of having falls in the past year (yes/no); (9) depression was measured using the 6-item Kessler Psychological Distress Scale (K6).

2-4 Other variables

Socio-demographic characteristics including age, gender, living alone (yes/no), smoking (current smoker or not), drinking (current drinker or not) and income status (enough or not) were collected using questionnaires. Polypharmacy was defined as taking 5 or more prescription medications (yes/no).

2-5 Statistical analyses

Descriptive data were summarized as means ± standard deviation for continuous variables and frequency (percentage) for categorical variables. Internal consistency was calculated by the Kuder-Richardson formula 20 (KR-20) with values above 0.70 indicating satisfactory internal consistency (Kuder and Richardson, 1937). Intraclass correlation coefficients (ICCs) were obtained to assess the test-retest reliability (15-day interval) in a sample of 44, with values above 0.70 indicating good test-retest reliability (Shrout and Fleiss, 1979). The coefficients of Phi (item vs dichotomous outcome), Point-Biserial (item vs outcome with normal distribution), and Spearman (item vs outcome without normal distribution) were calculated to evaluate the construct validity (Dancey and Reidy, 2007). It was expected that each item would show the highest correlation with its corresponding measures (convergent construct validity) and lower correlations with the measures of the other items (divergent construct validity). Diagnostic test accuracy (criterion validity) was evaluated by receiver operating characteristic curve (ROC) analysis using the FFP as a criterion. The area under the curve above 0.80 was judged to indicate good criterion validity (Murphy et al., 1987). The optimal cut-off point was determined by the maximum value of the Youden index. Cohen's kappa test was used to assess the level of agreement (0–0.20, slight; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, substantial; 0.81–1.00, almost perfect) between both scales and the FFP (Landis and

Koch, 1977). The concurrent validity was examined by the multivariate linear/logistic regression model. All the analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC), and the statistical significance level was set at $\alpha = 0.05$ in two-sided tests.

3. Results

3-1 Participant characteristics

The characteristics of the study population are shown in Table 3. Overall, 858 participants with a mean age of 70.89 were included. The prevalence for each item in the two scales were 103 (12.0%, FRAIL-J) and 106 (12.4%, FFPQ) for fatigue, 241 for resistance (28.1%), 54 for ambulation (6.3%), 0 for illness (0%), 136 for inactivity (15.9%), and 81 for loss of weight (9.4%). The prevalence of frailty defined by the FFP was 2.1%.

3-2 Reliability

The KR-20 coefficient was 0.32 for the FRAIL-J and 0.29 for the FFPQ. The test-retest reliability (ICCs) for the 15-day interval was 0.79 for the FRAIL-J and 0.72 for the FFPQ.

3-3 Construct validity

Table 4 summarizes the construct validity. The Spearman rank correlations ranged from -0.22 to 0.49 when correlating each item with outcome measurements. The convergent validity of fatigue, resistance, ambulation, and inactivity was good since each item showed the highest correlation with its corresponding measurement: fatigue in both scales was correlated with K6; both resistance and ambulation were correlated with physical performance; inactivity was correlated with EEPA and TST. Divergent validity was also good because these correlations were stronger than the correlations between the corresponding measurement and other items. Evidence for the construct validity of loss of weight did not appear since no significant correlation was found between loss of weight and BMI.

3-4 Criterion validity

Table 5 shows the diagnostic accuracy of both questionnaires. Compare with a 3-point cut-off, a 2-point cut-off identified a higher prevalence of frailty by FRAIL-J (12.5% vs 2.3%) and FFPQ (16.9% vs 3.8%). The AUCs for FRAIL-J and FFPQ were 0.86 and 0.88, respectively. The optimal cut-off for FRAIL-J was 2, with a higher Youden index (66.7% vs 20.3% for 3) and a high negative predictive value (NPV=99.5%) but a low positive predictive value (PPV=13.1%). As for the FFPQ, either 2 or 3 points were evaluated as the cut-off because the Youden index (62.2% vs 58.5%) and NPV (99.7% vs 99.2%) were similar but the PPV using a 2-point cut-off

was much lower (9.7% vs 33.3%). A Slight agreement was found between FFP and both questionnaires using a 2-point cut-off. Moderate agreement was found between FFP and FFPQ using a 3-point cut-off (kappa=0.42).

The concurrent validity of the two questionnaires is shown in Tables 6 and 7. Irrespective of whether a 2-point or 3-point cut-off was used in both questionnaires, participants with frailty showed lower gait speed, shorter time for one-leg standing, lower EEPA, worse cognitive function, higher K6 score, and a higher rate of falls. However, some differences between both questionnaires still existing. First, frailty status defined by the FRAIL-J showed lower grip strength. Second, frailty status defined by FFPQ showed stronger correlations with IADL and objectively measured TST. In addition, when using a 3-point cut-off, participants with frailty showed higher BMI, however, the trend was disappeared in the FFPQ when using a 2-point cut-off.

Table 4. Characteristics of the Total Sample

Characteristics	(Mean ± SD) or n (%)	Characteristics	(Mean ± SD) or n (%)
Age, year	70.9±3.2	MoCA score, point	24.3±2.9
Gender, men	414 (48.3)	K6 score, point	3.4±2.9
Living alone	86 (10.0)	IADL, difficulty ⩾1 task	44 (5.1)
Current drinker	432 (50.4)	Fall experience (past year)	143 (16.7)
Current smoker	65 (7.6)	Fatigue, FRAIL-J	103 (12.0)
Income, enough	448 (52.2)	Fatigue, FFPQ	106 (12.4)
Polypharmacy, ⩾5	134 (15.6)	Resistance	241 (28.1)
Education, year	12.9±2.4	Ambulation	54 (6.3)
BMI, kg/m^2	22.9±3.2	Illness, ⩾5	0 (0)
Grip strength, kg	29.3±8.2	Inactivity	136 (15.9)
Gait speed, m/second	1.5±0.3	Loss of weight	81 (9.4)
One-leg standing, second	83.3±42.6	Fried frailty phenotype	
EEPA, kcal/kg/day	9.8±2.7	Prefrail	341 (40.0)
TST, min/day	442.8±108.4	Frail	18 (2.1)

SD, Standard Deviation; BMI, Body Mass Index; EEPA, Energy Expenditure of Physical Activity; TST, Total Sedentary Time; MoCA, Montreal Cognitive Assessment; K6, 6-item Kessler Psychological Distress Scale; IADL, Instrumental Activity of Daily Living; FRAIL-J, Japanese FRAIL scale; FFPQ, Fried Frailty Phenotype Questionnaire, n=858.

Table 5. Correlations between Each Item and Cross-sectional Outcomes

Cross-sectional outcomes	Fatigue, FRAIL-J		Fatigue, FFPQ		Resistance		Ambulation		Inactivity		Illness		Loss of Weight	
	Correlation	*P* value	Correlation	*P* value	Correlation	*P* value	Correlation	*P* value	Correlation	*P* value	Correlation	*P* value	Correlation	*P* value
BMI*	0.12	0.001	0.01	0.82	0.10	0.002	0.08	0.021	0.06	0.11	--	--	-0.07	0.05
Grip strength#	-0.07	0.21	-0.06	0.10	-0.13	<0.001	-0.08	0.006	0.07	0.05	--	--	-0.02	0.56
Gait speed*	-0.10	0.004	-0.07	0.047	-0.16	<0.001	-0.22	<0.001	-0.06	0.07	--	--	-0.004	0.92
One-leg standing#	-0.11	0.001	-0.06	0.07	-0.19	<0.001	-0.13	<0.001	-0.04	0.26	--	--	-0.07	0.031
EEPA*	-0.08	0.022	-0.02	0.56	-0.09	0.008	-0.12	<0.001	-0.17	<0.001	--	--	0.06	0.10
TST*	-0.004	0.91	-0.01	0.68	0.02	0.54	0.02	0.53	0.17	<0.001	--	--	-0.05	0.17
MoCA#	-0.09	0.011	-0.08	0.017	-0.04	0.19	-0.09	0.012	-0.05	0.18	--	--	-0.08	0.015
K6#	0.21	<0.001	0.49	<0.001	0.10	0.002	0.13	<0.001	0.05	0.11	--	--	0.11	0.001
IADL§	0.03	0.41	0.12	<0.001	0.02	0.57	0.03	0.43	0.09	0.011	--	--	0.03	0.33
Fall experience§	0.12	<0.001	0.09	0.009	0.11	0.001	0.05	0.13	0.003	0.93	--	--	0.06	0.09

FRAIL-J, Japanese FRAIL scale; FFPQ, Fried Fried Frailty Phenotype Questionnaire; BMI, Body Mass Index; EEPA, Energy Expenditure of Physical Activity; TST, Total Sedentary Time; MoCA, Montreal Cognitive Assessment; K6, 6-item Kessler Psychological Distress Scale; IADL, Instrumental Activity of Daily Living, n=858.

*: Point-Biserial coefficient (item vs outcome with normal distribution) ; #: Spearman coefficient (item vs outcome without normal distribution); §: Phi coefficient (item vs dichotomous outcome).

Table 6. Diagnostic Accuracy of the FRAIL-J and FFPQ Using the Fried Frailty Phenotype as a Criterion

		Frail, n (%)	AUC (95% CI)	Youden Index, %	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Kappa
FRAIL-J									
	cut-off ⩾2	107 (12.5)	0.86* (95% CI: 0.75-0.96)	66.7	77.8	88.9	13.1	99.5	0.20*
	cut-off ⩾3	20 (2.3)		20.3	22.2	98.1	20.0	98.3	0.19
FFPQ									
	cut-off ⩾2	145 (16.9)	0.88* (95% CI: 0.79-0.97)	62.2	77.8	84.4	9.7	99.7	0.14*
	cut-off ⩾3	33 (3.8)		58.5	61.1	97.4	33.3	99.2	0.42#

FRAIL-J, Japanese FRAIL scale; FFPQ, Fried Frailty Phenotype Questionnaire; AUC, Area Under the Curve; CI, Confidence Interval; PPV, Positive Predictive Value; NPV, Negative Predictive Value. *P<0.001, #<0.01, n=858.

Table 7. Cross-sectional Associations for Frailty Status (cut-off ≥3) with Cross-sectional Outcomes

Cross-sectional outcomes	Frailty status[§]	FRAIL-J			FFPQ		
		β (SE)	*P* value	*P* for trend	β (SE)	*P* value	*P* for trend
BMI*	Pre-frail	0.68 (0.22)	0.003	<0.001	0.42 (0.22)	0.06	0.027
	Frail	1.80 (0.73)	0.013		0.72 (0.55)	0.20	
Grip strength*, kg	Pre-frail	-1.03 (0.52)	0.048	0.015	-0.41 (0.51)	0.42	0.08
	Frail	-2.98 (1.68)	0.08		-2.97 (1.34)	0.026	
Gait speed*, m/second	Pre-frail	-0.06 (0.02)	<0.001	<0.001	-0.05 (0.02)	0.001	<0.001
	Frail	-0.13 (0.06)	0.025		-0.18 (0.04)	<0.001	
One-leg standing*, second	Pre-frail	-14.21 (2.86)	<0.001	<0.001	-11.41 (2.80)	<0.001	<0.001
	Frail	-27.88 (9.24)	0.003		-25.25 (7.37)	<0.001	
EEPA[#], kcal/kg/day	Pre-frail	-0.26 (0.17)	0.14	0.031	-0.44 (0.17)	0.009	<0.001
	Frail	-1.16 (0.55)	0.036		-1.47 (0.44)	<0.001	
TST[#], min/day	Pre-frail	1.31 (6.33)	0.84	0.54	12.11 (6.15)	0.049	0.004
	Frail	21.10 (20.48)	0.30		44.48 (16.21)	0.006	
MoCA*	Pre-frail	-0.46 (0.20)	0.025	0.002	-0.53 (0.20)	0.008	0.002
	Frail	-1.78 (0.66)	0.007		-1.11 (0.52)	0.034	
K6*	Pre-frail	0.91 (0.20)	<0.001	<0.001	1.46 (0.19)	<0.001	<0.001
	Frail	2.02 (0.65)	0.002		3.37 (0.51)	<0.001	
		Odds Ratio (95% CI)			Odds Ratio (95% CI)		
IADL*, difficulty ≥1 task	Pre-frail	1.20 (0.61-2.37)	0.60	0.176	2.39 (1.17-4.87)	0.017	0.003
	Frail	4.79 (1.04-21.94)	0.044		6.03 (1.55-23.41)	0.010	
Fall experience*	Pre-frail	1.61 (1.10-2.36)	0.014	<0.001	1.22 (0.83-1.80)	0.30	0.012
	Frail	5.52 (2.11-14.50)	<0.001		3.75 (1.71-8.25)	0.001	

§, Pre-frail: cut-off=1 or 2, Frail: cut-off ⩾3; FRAIL-J, Japanese FRAIL scale; FFPQ, Fried Frailty Phenotype Questionnaire; SE, Standard Error; BMI, Body Mass Index; EEPA, Energy Expenditure of Physical Activity; TST, Total Sedentary Time; MoCA, Montreal Cognitive Assessment; K6, 6-item Kessler Psychological Distress Scale; IADL, Instrumental Activity of Daily Living. *Adjusted for age, gender, living alone, drinking, smoking, education, income, and polypharmacy; [#]Additional adjusted for wear time, n=858.

Table 8. Cross-sectional Associations for Frailty Status (cut-off ≥2) with Cross-sectional Outcomes

Cross-sectional outcomes	Frailty status[§]	FRAIL-J			FFPQ		
		β (SE)	*P* value	*P* for trend	β (SE)	*P* value	*P* for trend
BMI*	Pre-frail	0.66 (0.24)	0.007	0.001	0.50 (0.24)	0.038	0.09
	Frail	0.88 (0.34)	0.010		0.37 (0.31)	0.23	
Grip strength*, kg	Pre-frail	-0.66 (0.57)	0.24	0.006	-0.42 (0.55)	0.45	0.18
	Frail	-2.24 (0.79)	0.005		-0.93 (0.71)	0.19	
Gait speed*, m/second	Pre-frail	-0.03 (0.02)	0.10	<0.001	-0.04 (0.02)	0.035	<0.001
	Frail	-0.16 (0.03)	<0.001		-0.11 (0.02)	<0.001	
One-leg standing*, second	Pre-frail	-11.94 (3.12)	<0.001	<0.001	-10.72 (3.06)	<0.001	<0.001
	Frail	-22.04 (4.33)	<0.001		-15.82 (3.93)	<0.001	
EEPA[#], kcal/kg/day	Pre-frail	-0.13 (0.19)	0.49	0.012	-0.43 (0.18)	0.019	0.001
	Frail	-0.71 (0.26)	0.006		-0.68 (0.23)	0.004	
TST[#], min/day	Pre-frail	-2.06 (6.93)	0.77	0.34	10.81 (6.72)	0.11	0.008
	Frail	12.88 (9.62)	0.18		21.72 (8.64)	0.012	
MoCA*	Pre-frail	-0.47 (0.22)	0.033	0.011	-0.49 (0.22)	0.023	0.003
	Frail	-0.63 (0.31)	0.041		-0.74 (0.28)	0.008	
K6*	Pre-frail	0.58 (0.22)	0.009	<0.001	1.01 (0.20)	<0.001	<0.001
	Frail	1.94 (0.31)	<0.001		2.83 (0.26)	<0.001	
		Odds Ratio (95% CI)			Odds Ratio (95% CI)		
IADL*, difficulty ≥1 task	Pre-frail	1.13 (0.53-2.41)	0.75	0.24	2.32 (1.09-4.93)	0.029	0.007
	Frail	1.83 (0.73-4.59)	0.20		3.11 (1.29-7.55)	0.012	
Fall experience*	Pre-frail	1.46 (0.96-2.22)	0.08	<0.001	1.11 (0.73-1.70)	0.62	0.016
	Frail	2.51 (1.50-4.19)	<0.001		1.90 (1.18-3.07)	0.009	

§, Pre-frail: cut-off=1, Frail: cut-off ≥2; FRAIL-J, Japanese FRAIL scale; FFPQ, Fried Frailty Phenotype Questionnaire; SE, Standard Error; BMI, Body Mass Index; EEPA, Energy Expenditure of Physical Activity; TST, Total Sedentary Time; MoCA, Montreal Cognitive Assessment; K6, 6-item Kessler Psychological Distress Scale; IADL, Instrumental Activity of Daily Living. *Adjusted for age, gender, living alone, drinking, smoking, education, income, and polypharmacy; [#]Additional adjusted for wear time, n=858.

4. Discussion

In the present study, we developed a FRAIL-J and an FFPQ and evaluated the reliability and validity of both questionnaires in Japanese community-dwelling older adults. Both questionnaires showed low internal consistency, good test-retest reliability, acceptable construct validity, satisfactory diagnostic accuracy, and concurrent validity.

The KR-20 coefficients of both questionnaires were less than 0.70 indicating a low internal consistency. Similar results were also found in previous studies with values of 0.485 (Dong et al., 2018) and 0.447 (Aprahamian et al., 2017a), respectively. The low internal consistency could be explained by the existence of two sub-dimensions of FRAIL scale which are physical performance (ambulation and resistance) and health status (fatigue, weight loss, and illnesses), which seem to be associated with different socio-demographic and clinical characteristics suggesting different pathways to frailty (Aprahamian et al., 2017b). The ICCs of both questionnaires were higher than 0.70 indicating the stability of both scales across time.

The items of fatigue, resistance, ambulation, and inactivity showed good convergent and divergent validities, however, three issues must be further considered with respect to the construct validity. First, loss of weight did not correlate with BMI, as in a previous study (Gobbens et al., 2010). This could be because the item was

likely correlated to some indicators of change in weight over time. For example, previous studies observed the loss of weight was correlated with Mini-Nutritional Assessment which includes an assessment of weight loss (Dong et al., 2018, Rosas-Carrasco et al., 2016). Second, no participants met the definition of illness in the FRAIL-J. This could be because the IFS only recruited older adults aged 65-75 years, and people in a better physical state might have been more inclined to participate in the survey. Indeed, previous studies also showed a very low prevalence of illness in Korea (2.9%, patients aged 65 years or older) (Jung et al., 2016) and the United States (2.1%, African Americans aged 49-65 years) (Morley et al., 2012). Last, although our findings indicated that inactivity using 80% as the cut-off had good construct validity as expected, further studies are still needed to examine it in the more diverse populations.

Previous studies of the FRAIL scale mainly focused on its ability to predict adverse outcomes. Although such analysis is necessary for validity research, information on the diagnostic accuracy using a valid and reliable frailty instrument as a criterion is more useful in terms of health care. In the present study, using the FFP as a criterion, ROC analysis indicated both questionnaires had good diagnostic accuracy, higher than those of other versions of the FRAIL scale investigated in Brazil (AUC=0.68) (Aprahamian et al., 2017a) and Korea (AUC=0.77) (Jang et al., 2017), and similar to

that of a Chinese FRAIL scale (AUC=0.91) (Dong et al., 2018). A frailty screening tool needs to have a high sensitivity and high NPV to ensure all individuals at risk for frailty can be detected (Clegg et al., 2015). In the present study, compared with a 3-point, a 2-point cut-off for both questionnaires had higher sensitivity and higher NPV, while the PPV was low. In addition, a 2-point cut-off identified 12.5% of individuals with frailty as screened by FRAIL-J and 16.9% for FFPQ which are much higher than those defined by FFP (2.1%) in the present study and a recent meta-analysis. This meta-analysis showed that the age-stratified prevalence of frailty based on FFP in Japan was 1.9% and 3.8% for those aged 65-69 and 70-74 years, respectively (Kojima et al., 2017). It is notable that a 3-point cut-off of FFPQ showed the similar prevalence (3.8%) and might be also adopted for frailty screening given its comparable sensitivity (61.1%) and NPV (99.2%) to the 2-point cut-off, and a moderate agreement (kappa=0.42) with FFP. As a rapid screening instrument, our results suggesting a 2-point cut-off for both questionnaires or 3-point cut-off for FFPQ can be adopted, however, an elementary but important point is that both questionnaires cannot be expected to replace the FFP according to the results.

The associations between the two questionnaires and frailty status were similar to previous studies. Morley et al. (Morley et al., 2012) found participants with frailty showed lower gait speed, shorter time for one-leg standing, poorer Falls Efficacy

Scale, and lower mental health. A recent systematic review found that older adults with frailty had fourfold increased odds of depression (Soysal et al., 2017). As for EEPA, as we knew there is no study evaluating the association between EEPA and frailty status screened by the FRAIL scale until now. The results indicated that although the FRAIL-J does not include a question about physical activity, it also can discriminate participants with lower EEPA. Previous studies found the significant association between frailty defined by the FRAIL scale and IADL, however, no significant trend was found in the present study. These results might be explained by the deficiency of illness (no participants met the definition of this item). Moreover, these results may indicate that the existing definition of illness (e.g., type, severity, the number of diseases) may not be appropriate in Japan. Participants with frailty screened by the FFPQ showed higher TST, as might be expected since the FFPQ includes an item for assessing sedentary behavior. A recent study found that among older adults who are inactive and vulnerable or frail, TST increases mortality risk, but among those who are robust or active, TST does not affect the risk of mortality (Theou et al., 2017).

Frailty status defined by the FRAIL-J showed lower grip strength, while this result was not appeared using the FFPQ to define frailty. Indeed, previous studies also reported different results. Morley et al. (Morley et al., 2012) found that older adults

with frailty showed lower grip strength, however, a Chinese study found an opposed result (Woo et al., 2015). These results might be explained by two reasons. First, in the present study, including an item of inactivity (dichotomous) may decrease the discriminating ability of grip strength (no correlation was found between inactivity and grip strength, Table 4). Second, the grip strength may not be a good criterion for criterion validity test. Because the item of resistance was tested for the ability to climb stairs, one-leg standing or timed up-and-go test may be more suitable as an alternative criterion. The results in Table 4 also showed that the correlation of resistance with one-leg standing was higher than grip strength. As for the BMI, although older adults with frailty showed higher BMI when using 3-point cut-off of both questionnaires, the trend was disappeared in the FFPQ (*P* for trend from 0.027 to 0.09) when using a 2-point cut-off. Morley et al. (Morley et al., 2012) found that older adults with frailty showed higher BMI, however, the trend did not appear in a community-based study (Woo et al., 2015). Just like grip strength, including the item of inactivity in the FFPQ may decrease the discriminating ability of BMI. In addition, although fatigue in the FRAIL scale was directed at the exhaustion of FFP, when compared with each other, in addition to the K6, fatigued was more relevant to BMI and fall but exhaustion was more relevant to IADL (Table 4).

There are some limitations to this study. First, our participants were age-restricted to 65-75 years and geographically restricted to a single city in Japan. Therefore, the sample was not representative of the older Japanese population as a whole. Second, only 32.6% submitted questionnaires and 19.0% responded to the invitation to participate in further assessments. A healthier group might have self-selected for participation. Finally, the cross-sectional design precludes the ability to examine the predictive validity of the two questionnaires for adverse outcomes.

5. Conclusions

The FRAIL-J and FFPQ present acceptable reliability and validity and a 2-point cut-off of both questionnaires or a 3-point cut-off of the FFPQ can be used as the first step for frailty screening in Japanese community-dwelling older adults.

Chapter 3. Associations of objectively measured patterns of the sedentary behavior and physical activity with frailty status screened by the Japanese FRAIL scale and Fried Frailty Phenotype Questionnaire in Japanese community-dwelling older adults (study 2)

1. Introduction

Frailty is defined as a medical syndrome that can increase the risk of adverse outcomes. Meanwhile, previous studies have demonstrated that frailty is a dynamic condition and frailty status can transition between better and worse over time (Lee et al., 2014). This aspect of frailty presents an opening for potential preventative and restorative interventions. Lifestyle is considered one of the main keystones in the development of frailty, and a healthy lifestyle can help older adults to manage frailty. As a common component of lifestyle, daily sedentary behavior (SB) and physical activity (PA) may play an important role in the development of frailty (Kehler et al., 2018a, Kehler et al., 2018b).

One recent review summarized the epidemiological evidence concerning the impact of SB on frailty (Kehler et al., 2018b). In this review, all studies used subjective assessment of SB such as TV watching time or self-reported sedentary or inactive lifestyle found a significant negative association between SB and frailty indicted that promoting physical activity may be a feasible way to prevent frailty. However, the evidence of the association between objective assessment of SB and frailty was inconsistent. Of eight total studies that reported the association between objectively measured total sedentary time and frailty among community-dwelling older adults, only three studies found significant associations. One reason causing this

inconsistency might be most studies only captured the total sedentary time without consideration to SB patterns of how sedentary time is accumulated in prolonged uninterrupted bouts such as ≥ 10 min or ≥ 30 min. Indeed, increasing evidence showed that the different SB patterns might result in distinct health outcomes (Bellettiere et al., 2019, Diaz et al., 2017). To date, two studies investigated the association between SB patterns and frailty, but only limited features of sedentary patterns were included in these two studies. In the study of Toledo Healthy Study on Aging (THSA), no significant association was found between the duration of SB bouts lasting ≥ 10 min and the score of Frailty Trait Scale (Del Pozo-Cruz et al., 2017). However, a significant association was found between the duration of SB bouts lasting ≥ 30 min and the levels of frailty in females from the National Health and Nutrition Examination Survey (NHANES) (Kehler et al., 2018a, Kehler et al., 2019). Therefore, further studies are needed to examine whether the association between SB and frailty depends on the bout length definition.

As for the association between objective assessment of PA and frailty, a recent review found that a higher amount of total moderate-to-vigorous physical activity (MVPA) time was associated with frailty (Kehler and Theou, 2019). However, the PA patterns of how MVPA is accumulated in consecutive/sporadic bouts such as ≥ 10 min or < 10 min required to influence frailty is still unclear. Although WHO

recommended that older adults aged 65 years and older should accumulate at least 150 minutes of MVPA per week in bouts ≥ 10 min (WHO, 2010), meeting such recommendation may be challenging, especially in the older adult with frailty (Blodgett et al., 2015a). A recent systematic review found that both MVPA in bouts of ≥ 10 min and <10 min is associated with favorable health outcomes such as BMI, body fatness, and all-cause mortality, which suggest bouts of any duration may have health-enhancing effects (Jakicic et al., 2019). Accordingly, the recent U.S. guidelines that bouted or sporadic MVPA can provide important benefits and highlight the potential health benefits of light physical activity (LPA) in older adults (Piercy, K. L., 2018). However, it is still less clear how bouted or sporadic MVPA and LPA are related to frailty.

Japan has the largest proportion of the elderly population and has the most rapid aging rate than that of any other country, while the life expectancy is the highest in the world (Arai et al., 2015). Moreover, according to a recent systematic review and meta-analysis, the prevalence of frailty in Japan was lower than in other countries (7.5% vs 9.9%) (Kojima et al., 2017). Comprehensively examine the associations of objectively assessed different patterns of SB and PA with frailty in Japan may provide a unique insight into the management of frailty. Thus, the purposes of the present study were 1) to investigate if different SB, PA patterns and the number of steps are

associated with frailty status, and 2) to determine the optimal cut-off value of PA and SB variables and steps to discriminate between frailty and non-frailty in Japanese community-dwelling older adults.

2. Methods

2-1 Study participants

Cross-sectional data were derived from the baseline survey of the Itoshima Frail Study (IFS), which was carried out from September to December in 2017. The design of IFS has been described in detail elsewhere (Chen et al., 2019). Briefly, the IFS is an ongoing community-based prospective study in Itoshima City, located in northwest Japan. Its aiming is to explore modifiable lifestyle factors causing/protecting against frailty. The inclusion criteria of IFS were primary residents of I. city, aged 65-75 years, who were not certified as requiring nursing care by the National Long-term Care Insurance System. Of approximately 10,000 older adults, 5,000 were randomly selected according to the residential area, sex, and age. A set of study information sheets and questionnaires were mailed to subjects, inviting them to community centers for further assessments. Of the 5,000 individuals we contacted, 1,631 submitted questionnaires and 949 completed further assessments, for a response rate of 32.6% and 19.0%, respectively. Of the 949 subjects, we excluded 19 individuals who did not

have accelerometer data, 69 individuals with less than 4 days of valid accelerometer data, and 42 individuals with missing data of covariates (Figure 3). This study was approved by the Institutional Review Board of Kyushu University, Japan. All participants provided written informed consent.

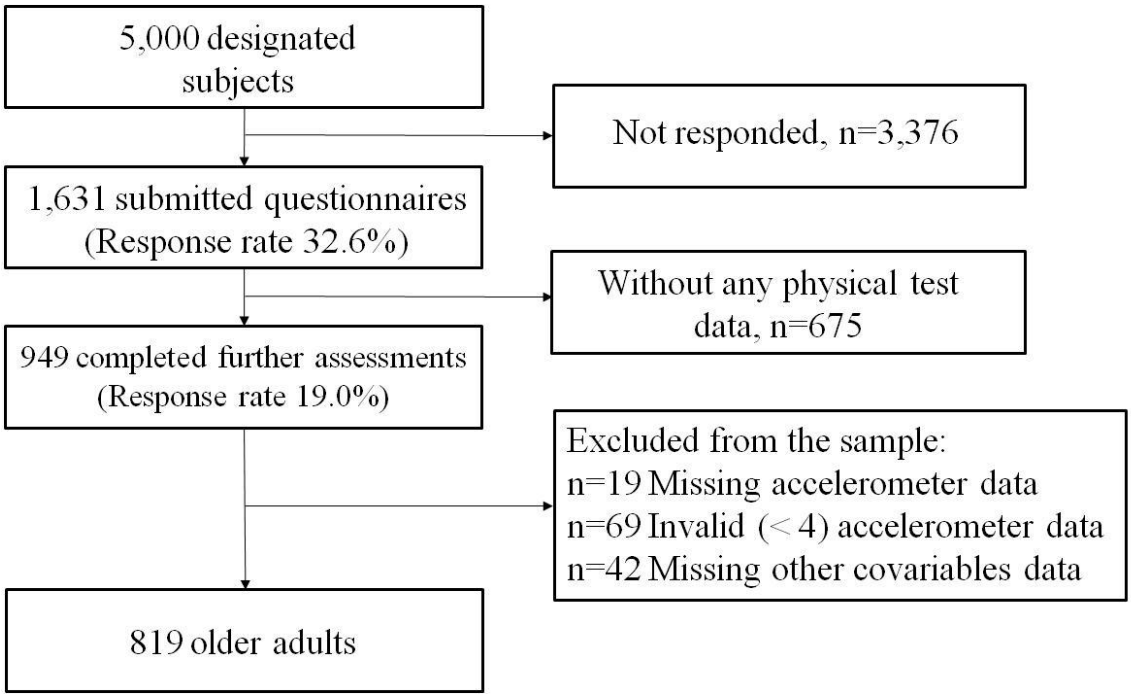

Figure 3. Flow chart of participation

2-2 Frailty screening

The Japanese FRAIL scale (FRAIL-J) and Fried Frailty Phenotype Questionnaire (FFPQ) (Table 2) were used to screen frailty status, which has shown good reliability and construct validity in our previous study (Chen et al., 2019). The total score of both questionnaires ranges from 0-5 points, with one point assigned to each component. Although the original FRAIL scale set a 3-point score as the cut-off point to identify frailty, our previous study showed that, compared to a 3-point cut-off, a 2-

point cut-off of both questionnaires had better criterion validity and could be the optimal one in Japanese older adults. Indeed, a 2-point cutoff for the FRAIL scale was also recommended in the Brazilian and Chinese versions (Aprahamian et al., 2017a, Dong et al., 2018). Therefore, in the present study, a score of 0 would indicate robust participants, 1 as pre-frailty, and 2-5 as frailty.

2-3 SB and PA variables

SB and PA were measured objectively using a waist-mounted, tri-axial, accelerometer (Active style Pro HJA-750C, Omron Healthcare, Kyoto, Japan) for seven consecutive days after the health assessment. The previous study reported that METs determined by the Active style Pro HJA-350IT were closely correlated with METs calculated by the indirect calorimetry, with an average percentage of differences less than 10%. Accordingly, the Active style Pro directly estimates the intensity of activities as METs (Ohkawara et al., 2011). Participants were instructed by trained personnel to wear the accelerometer on either side of their waist during their waking hours, and to remove the device only before going to bed or when engaging in water activities. Simple instruction and a log diary were also provided to encourage compliance with accelerometer protocols. Data were recorded in 60-s periods for the data analysis. The SAS macro program provided by the National Cancer Institute (National Cancer Institute, 2015) was modified for our accelerometer

to compute daily non-wear time, as described elsewhere (Chen et al., 2017, Honda et al., 2016). Non-wearing time was defined as at least 60 consecutive min of no activity, with an allowable 2 min to reach up to 1.0 metabolic equivalent (MET). Data for participants with at least 4 valid wear days (at least 10 h of wear time per day) were included in the analysis.

2-3-1 SB variables

Sedentary time was defined as a minute in which activity intensity was ≤ 1.5 METs, for example, resting in the sitting and lying or using computer (Ohkawara et al., 2011). A sedentary bout was defined as a period of sedentary time accumulated without interruption. Previous studies used 10 or 30 min/day as the cut-off value to define prolonged sedentary duration (Del Pozo-Cruz et al., 2017, Kehler et al., 2018a), however, the consensus is still lacking on the best measure of sedentary accumulation patterns. Therefore, apart from 10-min and 30-min bout of sedentary time, mean sedentary bout duration was also calculated by dividing total sedentary time by the total number of sedentary bouts in the present study, with higher values indicating more prolonged accumulation patterns, whereas lower values indicated more interrupted patterns.

2-3-2 PA variables

LPA was defined as activities of 1.5-3 METs such as laundry, dishwashing, or vacuuming (Ohkawara et al., 2011). MVPA was defined as activities of ≥ 3 METs including walking, jogging, and ascending or descending stairs (Ohkawara et al., 2011). Bouted MVPA was defined as ≥ 10 consecutive min, with an allowance for up to 2 min out of 10 to drop below the MVPA intensity threshold. This was consistent with the values recommended by the WHO physical activity guideline (WHO, 2010). Sporadic MVPA was defined as any MVPA accumulated in < 10 min. In addition, steps per day were also calculated.

2-4 Other variables

Socio-demographic characteristics including age, gender, education, living alone (yes/no), smoking (current smoker or not), and drinking (current drinker or not) were collected using questionnaires. Polypharmacy was defined as taking 5 or more prescription medications (yes/no). Cognitive function was measured using the Japanese version of the Montreal Cognitive Assessment (MoCA), conducted by the public nurses and trained staff. Instrumental activities of daily living (IADL) were measured using the 5-item subscale of the Tokyo Metropolitan Institute of Gerontology Index of Competence. The Japanese version of the Pittsburgh Sleep Quality Index (PSQI) was used to assess sleep.

2-5 Statistical Analysis

Descriptive data were summarized means ± standard deviation for continuous variables and as frequency (percentages) for categorical variables. Differences across frailty status were tested with the Jonckheere-Terpstra trend test for continuous variables, and the Cochran-Armitage trend test for categorical variables. In preliminary analyses, the effects of interaction between SB, PA variables and sex were examined by entering the interaction terms (exposure variables * sex) in age and sex adjusted logistic regression model and all interaction terms were not statistically significant (all $P > 0.05$). Therefore, all analyses were conducted with men and women together. Multivariable-adjusted multinomial logistic regression analyses were used to investigate the associations between SB, PA patterns and frailty status. The following two models were used to adjust for confounding factors: model 1 included age, sex, education, living alone, drinking and smoking status, polypharmacy, MoCA score, PSQI score, IADL, and accelerometer wear time; model 2 included factors in model 1 plus total MVPA time to SB variables (model 2a), or total sedentary time to PA variables (model 2b). In addition, in order to determine if bouted and sporadic MVPA independently associated with frailty status, sporadic MVPA and bouted MVPA were added to model 2c. The variance inflation factor (VIF) for all variables was calculated to detect the presence of colinearity. Each covariate had a VIF below 3 in the fully adjusted model 2, which is considered acceptable. Receiver operating

characteristic curve analysis (ROC) was used to define the cut-off value of time spent in specific levels of PA and SB variables to differentiate between being frailty and non-frailty when a significant association was observed in the logistic regression analysis. The area under the curve (AUC) represents the ability of a variable in differentiating between frailty and non-frailty. AUC values of > 0.80 are considered good, 0.70-0.79 fair, and < 0.70 poor (Metz, 1978). The optimal cut-off value was determined by the maximum value of the Youden index. ROC analyses were conducted using MedCalc version 19.1 (MedCalc Software, Ostend, Belgium) and other analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, N.C., USA). The statistical significance was set at $\alpha = 0.05$ in two-sided tests.

3. Results

The characteristics of the study population are presented in Table 8. Of the total 819 older adults, the mean age was 70.9 ± 3.1 years and a half were male (48.2%). In all participants, the prevalence of robust, pre-frailty and frailty defined by the FRAIL-J and FFPQ were 60.2% vs 50.0%, 27.8% vs 33.3%, and 12.0% vs 16.7%, respectively. On average, irrespective of whether FRAIL-J or FFPQ was used to screen frailty status, participants with frailty showed lower MoCA score, higher PSQI score, shorter total MVPA time and bouted MVPA, lower daily steps, and have a

higher ratio of polypharmacy. However, some inconsistent characteristics of frailty status screened by both questionnaires still existed. Frailty status screened by the FRAIL-J was more likely to be women, while this result was not observed using the FFPQ. In addition, Frailty status screened by the FFPQ showed longer mean sedentary duration, shorter sporadic MVPA, and a higher ratio of IADL, although these trends were not appeared using the FRAIL-J.

Table 9 shows the association between SB, PA variables and frailty status. In models 1 and 2, total sedentary time, 10-min and 30-min bout of sedentary time, and mean sedentary bout duration was not associated with pre-frailty and frailty screened by the FRAIL-J. Despite total sedentary time, 10-min and 30-min bout of sedentary time, and mean sedentary bout duration was associated with frailty screened by the FFPQ in model 1, these associations were disappeared after additional adjusted for the total MVPA time in model 2a. On the other hand, except LPA, PA variables including total MVPA time, sporadic MVPA, bouted MVPA, and steps were all significantly associated with frailty in model 1. However, the association between sporadic MVPA and frailty screened by both questionnaires, and the association between bouted MVPA and frailty screened by the FFPQ were disappeared after additional adjusted for the total sedentary time in model 2b. The final multivariable-adjusted odds ratios (95% confidence intervals) were 0.83 (0.75-0.92), 0.81 (0.70-0.92), and 0.80 (0.71-

0.89) for total MVPA time, bouted MVPA, and steps in the FRAIL-J and 0.91 (0.84-0.99), and 0.89 (0.82-0.98) for total MVPA time, and steps in the FFPQ. AUCs of total MVPA time, bouted MVPA, and steps were significant but only weak discriminations (all AUC < 0.7) were observed in the FRAIL-J. The optimal cut-off value of total MVPA time, bouted MVPA, and steps to discriminate between frailty and non-frailty were 43.25 min/day, 9.13 min/day, and 3841 steps/day, respectively (Figure 4). As for the FFPQ, all PA variables were significant but also only weak discriminations (all AUC < 0.7) were observed similar to the FRAIL-J. The optimal cut-off value of total MVPA time, sporadic MVPA, bouted MVPA, and steps to discriminate between frailty and non-frailty were 51.63 min/day, 11.0 min/day, 9.13 min/day, and 3702 steps/day, respectively (Figure 5).

Table 9. Characteristics of the Total Sample According to Frailty Status by the FRAIL-J and FFPQ

Variables	Total	Frailty Status			
		Robust	Pre-frailty	Frailty	*P* for trend
All					
FRIAL-J	819	493 (60.2)	228 (27.8)	98 (12.0)	
FFPQ		409 (50.0)	273 (33.3)	137 (16.7)	
Socio-demographic factors					
Age, year					
FRIAL-J	70.9±3.1	70.9±3.1	70.9±3.1	71.1±3.1	0.76
FFPQ		70.8±3.1	71.0±3.2	71.1±3.1	0.28
Gender, men					
FRIAL-J	395 (48.2)	254 (51.5)	105 (46.1)	36 (36.7)	0.006
FFPQ		201 (49.1)	134 (49.1)	60 (43.8)	0.36
Living alone					
FRIAL-J	80 (9.8)	44 (8.9)	26 (11.4)	10 (10.2)	0.44
FFPQ		35 (8.6)	32 (11.7)	13 (9.5)	0.47
Education, year					
FRIAL-J	12.9±2.4	12.9±2.4	12.9±2.3	12.7±2.3	0.39
FFPQ		12.9±2.4	13.1±2.3	12.7±2.4	0.75
Health behaviors factors					
Current drinker					
FRIAL-J	410 (50.1)	258 (52.3)	108 (47.4)	44 (44.9)	0.10
FFPQ		214 (52.3)	134 (49.1)	62 (45.3)	0.14
Current smoker					
FRIAL-J	59 (7.2)	44 (8.9)	9 (4.0)	6 (6.12)	0.07
FFPQ		37 (9.1)	17 (6.2)	5 (3.7)	0.025
Polypharmacy, ≥5					
FRIAL-J	126 (15.4)	53 (10.8)	43 (18.9)	30 (30.6)	<0.001
FFPQ		44 (10.8)	45 (16.5)	30 (30.6)	<0.001
IADL, ≥1					
FRIAL-J	41 (5.0)	22 (4.5)	11 (4.8)	8 (8.16)	0.19
FFPQ		11 (2.7)	19 (7.0)	11 (8.0)	0.003
MoCA score, point					
FRIAL-J	24.3±2.9	24.5±2.9	24.1±2.9	23.6±3.3	0.001
FFPQ		24.6±2.9	24.1±2.8	23.6±3.2	0.001
PSQI score, point					
FRIAL-J	4.1±2.8	3.8±2.6	4.2±3.0	5.3±3.2	<0.001
FFPQ		3.7±2.5	4.4±3.1	4.9±3.1	<0.001

Data shows mean ± SD or n (%). FRAIL-J, Japanese FRAIL scale; FFPQ, Fried Frailty Phenotype Questionnaire; IADL, Instrumental Activity of Daily Living; MoCA, Montreal Cognitive Assessment; PSQI, Pittsburgh Sleep Quality Index, n=819.

Table 9. Continue

Variables	Total	Frailty Status			
		Robust	Pre-frailty	Frailty	*P* for trend
Sedentary behavior and phycial activity					
Total sedentary time, min/day					
FRIAL-J	456.9 ±111.3	460.1 ±113.0	450.7 ±104.4	455.3 ±118.7	0.49
FFPQ		451.5 ±107.1	461.9 ±111.9	463.2 ±121.8	0.28
10-min bout of sedentary time, min/day					
FRIAL-J	328.1 ±113.8	331.2 ±115.6	321.5 ±105.1	327.7 ±124.1	0.65
FFPQ		321.2 ±107.7	334.1 ±115.3	337.0 ±127.3	0.11
30-min bout of sedentary time, min/day					
FRIAL-J	179.7 ±94.9	181.6 ±96.8	175.7 ±87.3	179.1 ±102.7	0.68
FFPQ		174.0 ±89.9	185.6 ±97.3	184.7 ±103.9	0.18
Mean sedentary bout duration, min/day					
FRIAL-J	4.11 ±0.73	4.12 ±0.74	4.07 ±0.69	4.12 ±0.80	0.87
FFPQ		4.06 ±0.70	4.15 ±0.74	4.17 ±0.80	0.047
Total LPA time, min/day					
FRIAL-J	341.0 ±94.4	339.6 ±93.5	342.9 ±91.3	343.2 ±102.1	0.60
FFPQ		347.9 ±90.1	335.7 ±95.4	333.9 ±103.9	0.06
Total MVPA time, min/day					
FRIAL-J	52.3 ±33.2	54.5 ±33.3	52.8 ±32.5	40.5 ±32.7	<0.001
FFPQ		55.7 ±33.0	50.9 ±33.7	45.4 ±31.9	<0.001
Sporadic MVPA, min/day					
FRIAL-J	31.4 ±17.9	32.0 ±18.1	31.6 ±16.9	27.9 ±18.9	0.14
FFPQ		33.0 ±18.2	30.8 ±17.8	27.8 ±16.9	0.004
Bouted MVPA, min/day					
FRIAL-J	20.9 ±24.1	22.5 ±24.1	21.2 ±25.1	12.7 ±20.5	<0.001
FFPQ		22.7 ±23.4	20.0 ±25.5	17.6 ±23.2	<0.001
Steps per day					
FRIAL-J	5652.9 ±2803.3	5872.2 ±2699.7	5695.1 ±2792.8	4451.7 ±3057.0	<0.001
FFPQ		5954.0 ±2637.7	5524.8 ±2817.6	5009.5 ±3129.6	<0.001

Data shows mean ± SD or n (%). FRAIL-J, Japanese FRAIL scale; FFPQ, Fried Frailty Phenotype Questionnaire; LPA, Light Physical Activity; MVPA, Moderate to Vigorous Physical Activity, n=819.

Table 10. Characteristics of the Total Sample According to Frailty Status by the FRAIL-J and FFPQ

Variables	Pre-frailty vs Robust (95% CI)		Frailty vs Robust (95% CI)	
	Model 1	Model 2	Model 1	Model 2
FRAIL-J				
Sedentary behavior				
Total sedentary time, increment per 30 min/day	0.99 (0.94-1.05)	0.97 (0.91-1.04)[a]	1.05 (0.97-1.13)	0.95 (0.86-1.04)[a]
10-min bout of sedentary time, increment per 30 min/day	0.99 (0.94-1.04)	0.98 (0.93-1.03)[a]	1.04 (0.97-1.11)	0.98 (0.90-1.05)[a]
30-min bout of sedentary time, increment per 30 min/day	1.00 (0.94-1.05)	0.99 (0.93-1.00)[a]	1.04 (0.96-1.13)	0.98 (0.90-1.07)[a]
Mean sedentary bout duration, increment per 1 min/day	0.97 (0.77-1.23)	0.95 (0.75-1.21)[a]	1.14 (0.83-1.58)	1.00 (0.72-1.40)[a]
Physical activity				
Total LPA time, increment per 10 min/day	1.01 (0.99-1.03)	1.01 (0.99-1.03)[a]	1.00 (0.97-1.03)	1.02 (0.99-1.05)[a]
Total MVPA time, increment per 10 min/day	0.98 (0.94-1.03)	0.97 (0.91-1.03)[b]	0.86 (0.79-0.93)**	0.83 (0.75-0.92)**[b]
Sporadic MVPA, increment per 10 min/day	0.99 (0.90-1.09)	0.96 (0.85-1.09)[b]	0.86 (0.74-0.99)*	0.84 (0.71-1.01)[b]
		0.97 (0.85-1.09)[c]		0.88 (0.73-1.05)[c]
Bouted MVPA, increment per 10 min/day	0.97 (0.91-1.04)	0.97 (0.90-1.04)[b]	0.80 (0.70-0.91)**	0.80 (0.69-0.91)**[b]
		0.97 (0.90-1.04)[c]		0.81 (0.70-0.92)**[c]
Step, increment per 1000 step/day	0.98 (0.92-1.04)	0.97 (0.90-1.03)[b]	0.82 (0.74-0.90)**	0.80 (0.71-0.89)**[b]
FFPQ				
Sedentary behavior				
Total sedentary time, increment per 30 min/day	1.05 (0.99-1.10)	1.03 (0.96-1.09)[a]	1.08 (1.01-1.16)*	1.03 (0.95-1.12)[a]
10-min bout of sedentary time, increment per 30 min/day	1.05 (0.99-1.10)	1.03 (0.98-1.09)[a]	1.08 (1.02-1.15)*	1.04 (0.98-1.12)[a]
30-min bout of sedentary time, increment per 30 min/day	1.05(0.99-1.11)	1.04 (0.98-1.10)[a]	1.07 (1.00-1.15)*	1.04 (0.96-1.12)[a]
Mean sedentary bout duration, increment per 1 min/day	1.22 (0.97-1.54)	1.18 (0.94-1.49)[a]	1.35 (1.01-1.81)*	1.24 (0.92-1.67)[a]
Physical activity				
Total LPA time, increment per 10 min/day	0.99 (0.97-1.01)	0.99 (0.97-1.01)[a]	0.98 (0.97-1.01)	0.99 (0.96-1.02)[a]
Total MVPA time, increment per 10 min/day	0.96 (0.91-1.00)	0.97 (0.91-1.03)[b]	0.90 (0.84-0.96)**	0.91 (0.84-0.99)*[b]
Sporadic MVPA, increment per 10 min/day	0.94 (0.86-1.03)	0.98 (0.87-1.11)[b]	0.83 (0.73-0.95)*	0.86 (0.73-1.01)[b]
		0.98 (0.87-1.11)[c]		0.87 (0.74-1.02)[c]
Bouted MVPA, increment per 10 min/day	0.95 (0.89-1.01)	0.96 (0.90-1.03)[b]	0.90 (0.82-0.99)*	0.92 (0.84-1.02)[b]
		0.96 (0.90-1.03)[c]		0.93 (0.85-1.02)[c]
Step, increment per 1000 step/day	0.94 (0.89-0.99)*	0.95 (0.89-1.02)[b]	0.88 (0.81-0.95)*	0.89 (0.82-0.98)*[b]

FRAIL-J, Japanese FRAIL scale; FFPQ, Fried Frailty Phenotype Questionnaire; Light Physical Activity; MVPA, Moderate-to-Vigorous Physical Activity.
Model 1, adjusted for age, sex, education, living alone, drink and smoke status, polypharmacy, MoCA score, PSQI score, IADL, and wear time.
Model 2, a, additional adjusted total MVPA time; b, additional adjusted total sedentary time; c, additional adjusted bouted MVPA and sporadic MVPA.
*, $P<0.05$; **, $P<0.01$. n=819.

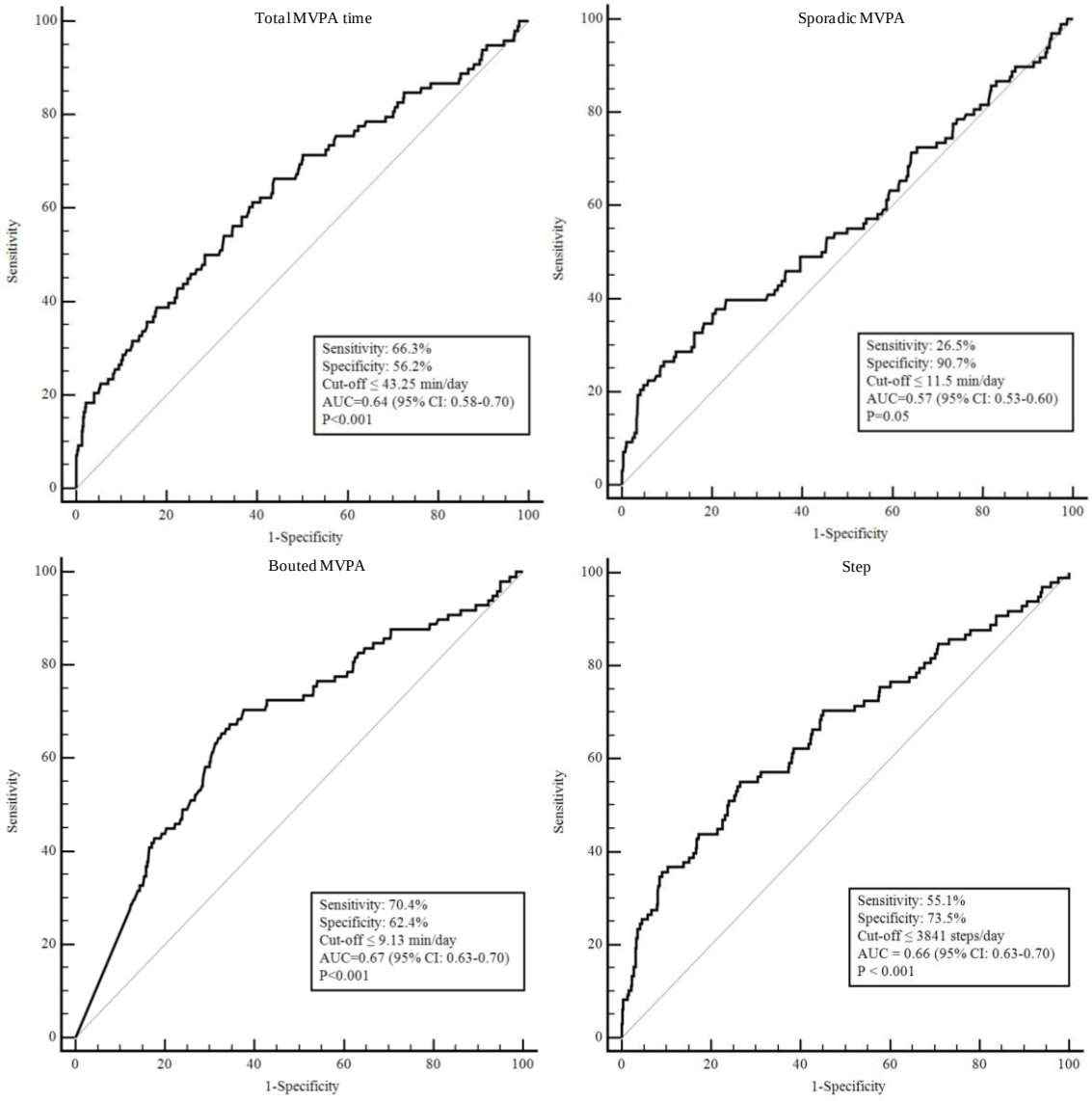

Figure 4. Receiver operating characteristic curves showing the optimal cut-off value of PA variables to discriminate frailty and non-frailty defined by the FRAIL-J in Japanese community-dwelling older adults. AUC, Area under the curve.

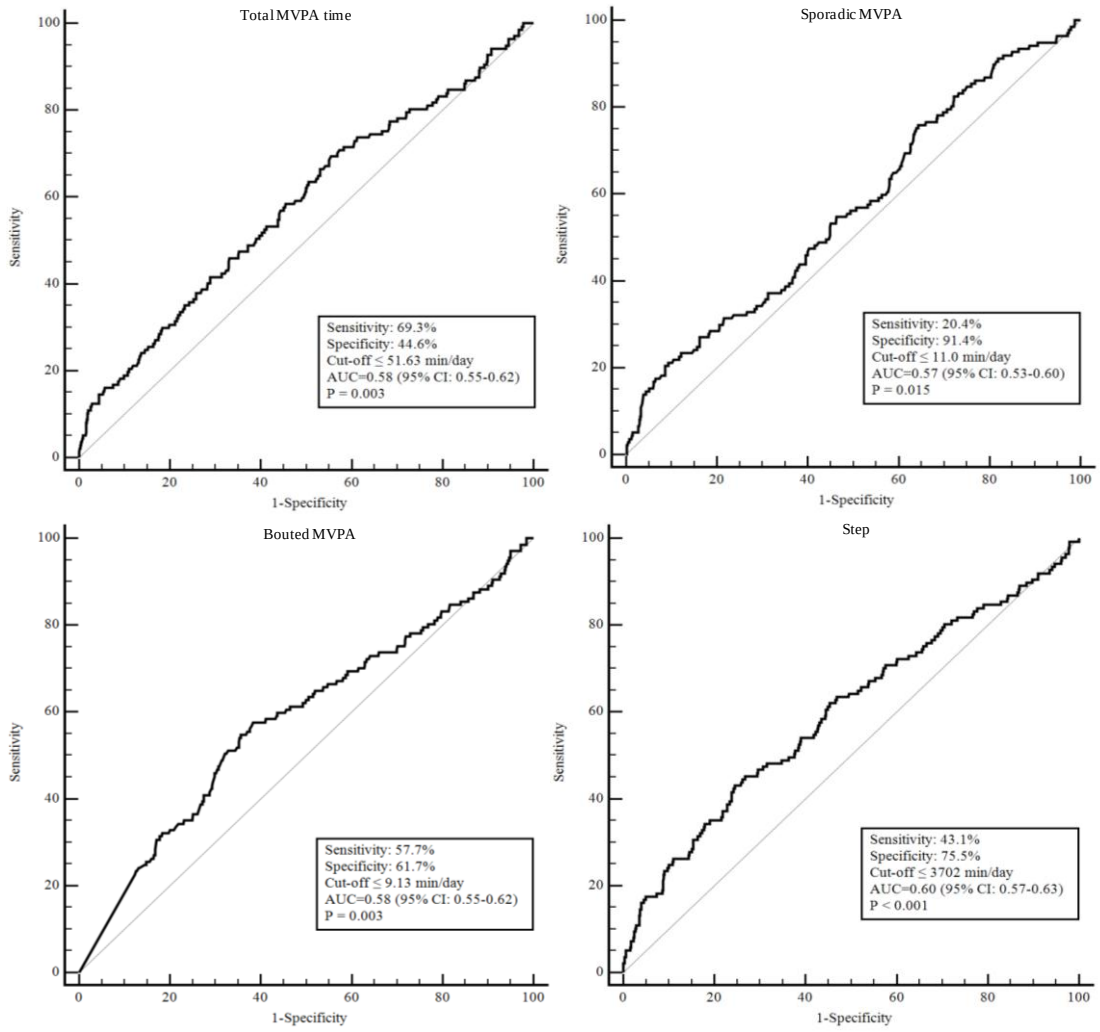

Figure 5. Receiver operating characteristic curves showing the optimal cut-off value of PA variables to discriminate frailty and non-frailty defined by the FFPQ in Japanese community-dwelling older adults. AUC, Area under the curve.

4. Discussion

To our knowledge, this is the first study to investigate the associations between objectively measured patterns of SB, PA and frailty status screened by the FRAIL-J in Japanese community-dwelling older adults. We found that neither the total sedentary time nor SB patterns were associated with pre-frailty or frailty. Higher levels of total MVPA time, bouted MVPA, and steps were not associated with pre-frailty but associated with frailty. However, the association of LPA and sporadic MVPA with frailty was not observed. In addition, our results suggest that 43.25 min/day of total MVPA, 9.13 min/day of bouted MVPA, and 3841 steps/day of daily step represent the optimal cut-off value to discriminate between frailty and non-frailty. The main findings in this study provide evidence concerning how objective PA patterns are associated with frailty which might inform future feasible approaches to managing frailty in older Japanese adults.

The associations between total sedentary time, 10-min bout of sedentary time and frailty defined by both questionnaires found in the present study are consistent with some previous studies (Bastone Ade et al., 2015, Castaneda-Gameros et al., 2018, Jansen et al., 2015, Manas et al., 2018, Nagai et al., 2018) while several inconsistencies are still observed. In contrast to the previous studies (Blodgett et al., 2015a, Del Pozo-Cruz et al., 2017, Song et al., 2015), the present study showed that

total sedentary time was not associated with frailty. Moreover, although a previous study has reported an inverse association between 30-min bout of sedentary time and 46-item frailty index (FI) in females, no such negative association was observed in the present study (Kehler et al., 2019). The reasons for the discrepancies between these findings and our results are multifaceted. First, participant characteristics may contribute to the discrepancies. For example, the present study only recruited older adults aged 65-75 years, while previous studies also include older adults aged more than 75 years. Second, the different objective measures of SB might be another reason. The present study used a tri-axial accelerometer to assess SB, which may more accurate than a uni-axial accelerometer used in previous studies (Blodgett et al., 2015a, Kehler et al., 2018a, Song et al., 2015). Third, the heterogeneity of frailty assessments between the present study and previous studies might be an important reason contributes to the inconsistencies. Aguayo et al. (Aguayo et al., 2017) examined the agreement between 35 frailty instruments found that marked heterogeneity existed among various frailty instruments. The fourth possible reason is regarding adjustment variables. Different factors inputted in the regression model might affect the final results. For example, total MVPA time was added to the final model to determine the independency of total sedentary time, while some previous studies did not add it (Del Pozo-Cruz et al., 2017, Song et al., 2015). Last, the

inconsistencies also might be explained by lifestyle differences between Western counties and Japan. Since Japan is unique in its healthy Japanese food and environment and health insurance system, enhanced awareness about healthy aging among the general public and made some difference in frailty status than other counties. Just like the so-called Japanese smoking paradox that Japanese people smoke more but develop less lung cancer than other populations. In a recent study, Liao et al. also found an inconsistent association of objective SB with performance-based physical function between American and Japanese older adults might be caused by cultural differences (Liao et al., 2018). Thus, further studies should be conducted using a same method to assess SB and frailty to clarify the association between objective SB and frailty in different settings.

Although our results found that higher total MVPA time had an association with a reduction in frailty, the optimal cut-off value (43.25 or 51.63 min/day) in the present study was much higher than the previous study which found total MVPA time of at least 7.5 minutes per day can prevent frailty development among 401 older adults aged 65-82 years (Yuki et al. 2019). One reason why the discrepancy appears might be caused by the different methods of how to define the cut-off value (25th percentile vs ROC analysis). Another main reason might be because the sporadic MVPA which is an essential part of total MVPA time was not associated with frailty in the present

study. LPA could be relatively easier to perform for older adults than MVPA and recent guidelines also highlight the potential ability of LPA to benefit the health of older adults (Piercy, K. L., 2018). However, no significant association between LPA and frailty was observed in the present study. Actually, due to the lack of evidence, the recommendations of LPA such as time and frequency are still unclear, more studies are needed to determine the role and contribution of LPA alone or in combination with MVPA to health outcomes. A recent harmonized meta-analysis study observed non-linear, dose-response associations between PA variables and mortality, the maximal risk reductions for LPA (0.48, 0.38 to 0.63) was observed at 375 min/day, while at 24 min/day for MVPA (0.39, 0.26 to 0.59) (Ekelund, U., 2019). Therefore, according to the above evidence and our results, we considered that MVPA might be a much better choice than LPA for frailty management in Japanese community-dwelling older adults.

In the present study, our results showed that sporadic MVPA was not associated with frailty defined by both questionnaires. This finding was opposed to a previous cross-sectional study from NHANES that demonstrated sporadic MVPA was associated with a 46-item frailty index (Kehler et al. 2018a). Although there has been an increasing number of studies demonstrated the positive associations between sporadic MVPA and adverse outcomes such as all-cause mortality and multimorbidity,

a recent review found that there are still some studies found only bouted MVPA but not sporadic MVPA was positively associated with adverse outcomes such as incidence of obesity and high-density lipoprotein cholesterol (Jakicic et al. 2019). An opposed result regarding the association between bouted MVPA and frailty was found between the FRAIL-J and FFPQ. Bouted MVPA was associated with frailty defined by the FRAIL-J after additional adjusted for total sedentary time and sporadic MVPA, while the association was not observed using the FFPQ. The main reason causing this result might be because of the inclusion of the inactivity item (dichotomous) in the FFPQ, which was assessed using a simple yes/no question: "Does your sitting or lying time account for 80% or more of your waking time?". Although our results showed that the inclusion of this item in the FFPQ partly increased its discriminating ability of SB (Table 4), it may decrease the discrimination of bouted MVPA. Further studies should be conducted to confirm these results. According to the results from the FRAIL-J, bouted MVPA might be more effective on frailty compared to sporadic MVPA. The benefits of sporadic MVPA positively impact health might be because of its contribution to adding total energy expenditure (Tremblay et al. 2007). Therefore, further study should be conducted to examine the effects of sporadic and bouted MVPA on adverse outcomes under the same total energy expenditure. The optimal cut-off value of bouted MVPA to discriminate between frailty and non-frailty defined

by both questionnaires was 9.13 min/day, which suggests that lower amounts of bouted MVPA (e.g. 70 minutes per week), compared to the recommendation of the WHO, might be an achievable initial target in older adults.

As the basic component of PA, daily step is an easy-to-understand metric. A recent systematic primary literature review found that an inverse dose-response relationship of daily steps with important health outcomes, including all-cause mortality, cardiovascular events, and type 2 diabetes (Kraus et al., 2019). In the present study, our findings showed that higher daily steps were negatively associated with frailty defined by both questionnaires. The optimal cut-off value of step to discriminate between frailty and non-frailty was 3841 steps per day for the FRAIL-J and 3702 steps per day for the FFPQ, which was lower than the suggestion (5000 steps/day) of recently prospective study among Japanese older adults (Yuki et al. 2019). The discrepancy might be caused by the difference in study populations and statistical analyses such as the difference between 25th percentile and ROC analysis.

Taken together, our findings indicated that lower amounts of bouted MVPA and steps can also benefit the health of older adults. It is more achievable and feasible compared to the official recommendations that make it be an initial target for older adults. These interesting findings point out a potential intervention method that combines bouted MVPA and steps together. For example, do a 10 min walking of any

speed inside or outside every day may be a simple but effective way to manage frailty. However, this value should be further confirmed among older adults in future intervention studies before these observations can be translated into public health guidelines.

There are some limitations to this study. One main limitation was the response bias which relates to the generalizability of the present findings. Participants in this study population were individuals 65 - 75 years old from just one southwest city in Japan and therefore it was not representative of the older Japanese population. In addition, the response rate was relatively low which could cause bias in interpreting the results since the participants that self-selected to participate in the study may be different from those who did not. For example, a healthier group might have been included in the present study because participants had to attend the community center for assessing physical and cognitive function. Moreover, the cross-sectional design of this study precludes the ability to examine the predictive ability to make causal inferences.

5. Conclusion

In conclusion, our findings demonstrate a strong relationship between higher levels of total MVPA time, steps and frailty screened by the FRAIL-J and FFPQ. Lower amounts of bouted MVPA (70 min/week) or steps (4000 steps/day) may be achievable

initial targets in older adults for frailty management. This evidence might inform the future of feasible approaches to managing frailty in Japanese community-dwelling older adults.

Chapter 4. Using the Fried Frailty Phenotype Questionnaire to assess the effects of an exercise intervention on frailty status in Japanese community-dwelling older adults (study 3)

1. Introduction

Frailty is a dynamic condition and frailty status can transit better or worsen over time (Lee et al., 2014). This characteristic of frailty presents an opening for potential preventative and restorative interventions. Recently, there is a growing body of studies to examine the effect of various types of interventions on frailty status. The exercise intervention was the most commonly used (Cesari et al., 2015, Chan et al., 2012, Jang et al., 2018, Kim et al., 2015, Luger et al., 2016, Nagai et al., 2018, Ng et al., 2015, Serra-Prat et al., 2017, Tarazona-Santabalbina et al., 2016) and has been proved as the most effective approach in reversing frailty although the detailed exercise program was not consistent (Kim et al., 2015, Ng et al., 2015). This reason may be because frailty is the result of the dysregulation of the well-tuned complex dynamical system of a resilient organism while exercise can simultaneously up-regulate many systems that mutually regulate each other in combination make the whole organism could be returned to a higher functional level (Fried, 2016).

To date, among the frailty exercise intervention studies, almost all of the researches used the Fried Frailty Phenotype (FFP) to assess the frailty status might be because the FFP has a solid foundation of the biological theoretical basis (Fried et al., 2001, Xue et al., 2008). The rapid and accurate assessment of one exercise intervention effect on frailty at frequent intervals is necessary for frailty management. Despite the

FFP was widely used in the intervention study and most of these studies demonstrated exercise could improve frailty status, it is still difficult to implement in large-scale intervention settings or evaluate at a frequent interval, as it requires objective measurement and population reference values that makes it impossible to self-evaluate. As a simpler alternative, the Fried Frailty Phenotype Questionnaire (FFPQ) was a simple self-reported frailty screening instrument and specially designed for screening the FFP in the large-scale epidemiological settings. The reliability and validity of the FFPQ have been well-validated and demonstrated it could be used as a frailty screening instrument in Japanese community-dwelling older adults (Chen et al., 2019). However, it is unclear whether the FFPQ could be used as an instrument to assess the effect of a frailty intervention. Therefore, the purpose of the study was to evaluate whether the FFPQ could be used as an instrument to assess the effect of an exercise intervention on frailty in Japanese community-dwelling older adults.

2. Methods

2-1 Study design and participants

A single-group, pre-test, post-test design was utilized in the present study. The study population was recruited from the Itoshima Frail Study (IFS), a community-dwelling based prospective cohort aiming is to explore modifiable lifestyle factors

causing/protecting against frailty (Chen et al., 2019). The FFP used in the IFS includes 5 components: shrinking, weakness, exhaustion, slowness, and low physical activity. The total score ranges from 0 to 5, participants scoring 3 to 5, 1 to 2, and 0 are designated frail, pre-frail and robust, respectively. Of the 949 older adults who participated in the whole assessment of the IFS, 388 (40.9%) and 22 (2.3%) of them were defined as pre-frailty and frailty by the FFP, respectively. A set of study information sheets detailing the aims, methods, and use of personal data were mailed to these older adults with pre-frailty or frailty that inviting them to community centers for the further multicomponent exercise intervention study. Of the above 410 individuals we contacted, 189 responded and volunteered as the participants in this study. Participants were assessed their physical condition by the doctor, and all of them were allowed to attend the multicomponent exercise. A 6-month series of 60 min/week multicomponent exercise was given to the 189 participants from September 16, 2018, to March 18, 2019. According to the purpose of this study, of the initial 189 participants, 77 individuals who did not meet the definition of the FFPQ, which also has five items directly to the definition of FFP (fatigue vs exhaustion, resistance vs weakness, ambulation vs slowness, inactivity vs low physical activity, and loss of weight vs shrinking) (Chen et al., 2019), were excluded from the analyses. Moreover, during the intervention, 8 individuals withdrew because of personal reasons. A

followed-up after the 6-months intervention was also conducted, and 16 individuals with missing accelerometer, physical, or other data of post-intervention were also excluded from the analyses (Figure 6). Finally, a total of 88 individuals (11 frail and 77 pre-frail defined by the FFPQ) with all valid data were included in the analyses. This study was approved by the Institutional Review Board of Kyushu University, Japan. All participants provided written informed consent.

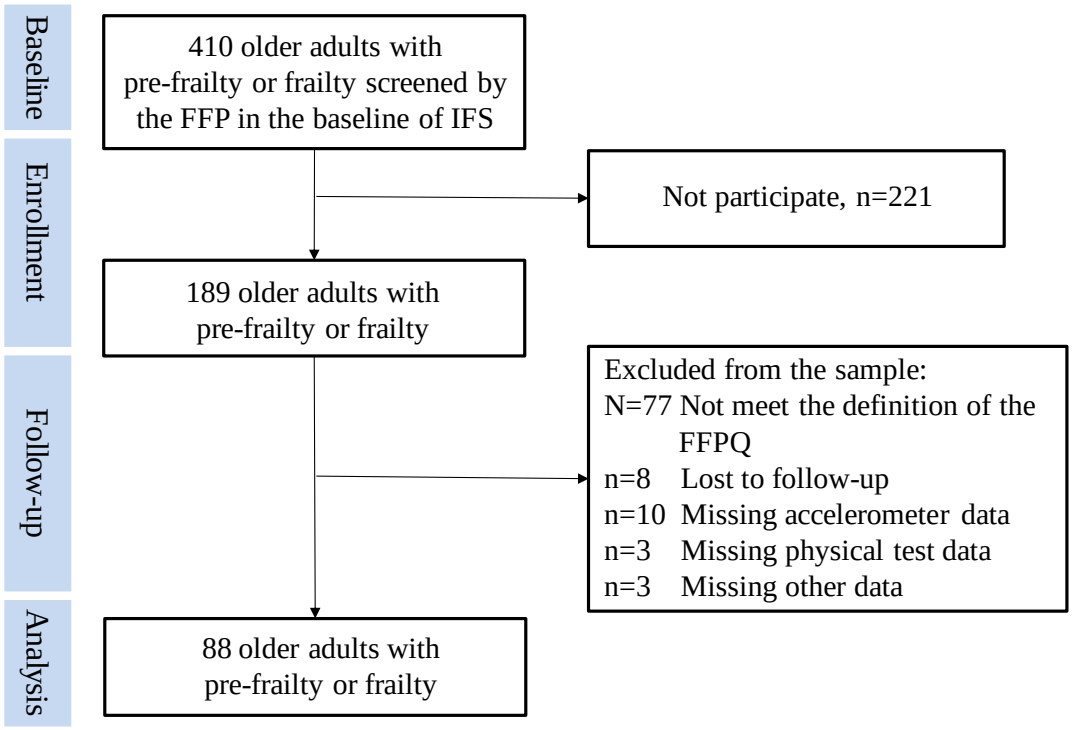

Figure 6. Flow chart of participation

2-2 Multicomponent exercise intervention

A set of a multicomponent exercise intervention program that has the potential to impact the functional performance measures was developed by substantially experienced instructors. This entire program consisted of 60 minutes of combined

warm-up, resistance, balance, stretching, and deep breathing, which named "Itoshima Frail Preventive Gymnastics". The warm-up exercises including six motions such as wrist, shoulder, and knee rotation. After warm-up exercises, 24 combined resistance and balance motions from easier to advanced were given to all the participants. Considering the older adults with pre-frailty or frailty may have worse physical functions, in the first 12 weeks, almost all the motions began with seated exercises. For the subsequent 12-24 weeks, all the motions advanced to a standing pose without the chair and yoga mat. Stretching and deep breathing were also performed at the end of the program. Participants were supervised by instructors with substantial resistance experience, to ensure consistent, safe activity. These exercise intervention classes performed 4 days per week at three community centers in Itoshima city to ensure the older adults can participate in the intervention once a week during their free time. In addition to the exercise intervention class once a week, a 10-min short version of the "Itoshima Frail Preventive Gymnastics" also including warm-up, resistance and balance, and stretching exercises as homework which has been well introduced and trained in the intervention class were also asked to be done every day step by step. A notebook including log sheets every day and exercise instruction with detailed pictures and descriptions were also provided to encourage compliance with protocols.

2-3 Outcome measurements

Outcome measurements including (1) FFP (2) FFPQ (3) body mass index (BMI); (4) muscle mass was measured through a bioelectrical impedance analysis machine (MC-180, Tanita, Tokyo), appendicular skeletal muscle mass (ASMM) was calculated as the sum of skeletal muscle in the arms and legs and the skeletal muscle mass index (SMMI) was defined as ASMM divided by body height in meters squared; (5) depression was measured using the 6-item Kessler Psychological Distress Scale (K6); (6) grip strength; (7) 5-time chair sit-to-stand test was measured using a stop watch, participants were asked to stand up from a sitting position and then to sit down 5 times as fast as possible; (8) gait speed, based on the time for a 5-meter walking test at one's maximum and normal walking speed; (9) open-eyed one-leg standing test (max=120sec); (10) regular physical activity including energy expenditure of physical activity (EEPA), total sedentary time (TST), light physical activity (LPA), moderate to vigorous physical activity (MVPA), and steps were objectively measured by a tri-axial accelerometer (Active style Pro HJA-350IT, Omron, Kyoto, Japan), participants were instructed to wear the accelerometer for consecutive 7 days and to remove the accelerometer only before going to bed or water activities. Participants with ≥ 3 valid days in which a valid day was defined by wearing the tri-axial accelerometer for more than 600 minutes were eligible for analysis. The daily percentage of TST, LPA, and MVPA were calculated by dividing TST, LPA, and MVPA time by the wear time.

2-4 Statistical analysis

Descriptive data were summarized as means ± standard deviation for continuous variables and frequency (percentage) for categorical variables. Comparisons of the characteristics between the excluded and included samples were used independent-sample t-test for comparing means and Pearson x^2 for comparing proportions. The changes in health measurements before and after the multicomponent exercise intervention were examined by paired-samples t-test. The agreement of using the FFP and FFPQ to assess the effects of intervention was examined by Cohen's kappa test (0–0.20, slight; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, substantial; 0.81–1.00, almost perfect) (Landis and Koch, 1977). The coefficients of Spearman were calculated to evaluate the correlations between the score changes of each item and the changes of each measurement before and after the intervention. It was expected that the score changes of each item would show the highest correlation with the changes of its corresponding measurement. All the analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC), and the statistical significance level was set at $\alpha = 0.05$ in two-sided tests.

3. Results

3-1 Baseline characteristics

The comparisons of the characteristics between the excluded and included samples in this study are shown in Table 10. Except for the K6 score, there was no significant difference between the excluded and included group regarding outcomes. The K6 score in the included group (5.56±3.86) was significantly higher than that in the excluded group (4.11±3.37).

3-2 Intervention effects on outcomes measurements

The results of the comparison of overall outcomes measurements before and after the multicomponent exercise intervention are presented in Table 11. The exercise intervention was very effective in lowering the frailty score of the FFP and FFPQ. The difference value (95% confidence intervals, 95% CI) of the pre- and post-intervention was -0.68 (-0.83, -0.54) and -0.73 (-0.95, -0.51), respectively. Except for the weakness in the FFP, and ambulation and inactivity in the FFPQ, other scores of the items in both instruments were significantly decreased after the intervention. As for the physical functions, 5-time chair sit-to-stand time, maximum and normal gait speed, and one-leg stand time were significantly improved with the intervention. However, grip strength did not show this improvement after intervention. We found an improvement in depression as the K6 score was significantly reduced. The exercise intervention did not change the EEPA and daily percentage of LPA, MVPA, and TST. Only steps per hour were increased by 62.5 (22.9, 102.1) after the intervention.

Moreover, exercise resulted in an increase in the BMI of participants but not increased the SMMI.

3-3 Agreement of using the FFP and FFPQ to assess the effect of the intervention

Table 12 shows the agreement of using the FFP and FFPQ to assess the effect of the intervention. A moderate Spearman correlation (rho=0.42) and fair agreement (kappa=0.35) of the intervention effect were found between the two instruments. Moreover, our results showed that 55.7 % (49 participants) for the FFP and 40.9 % (36 participants) for the FFPQ of the total sample, frailty was reversed (from pre-frail or frail to robust) after the exercise intervention.

3-4 Correlations between the change of each item and outcome measurements

Table 13 summarizes the correlations between the change of each item and the change of outcome measurements. The Spearman rank correlations ranged from −0.48 to 0.46 when correlating the change of each item with the change of outcome measurements. The item of exhaustion, weakness, slowness, and low physical activity in the FFP and the item of fatigue, resistance, and inactivity in the FFPQ could use to assess the effect of intervention since the change of each item showed the highest correlation with the changes of its corresponding measurements: exhaustion/fatigue was correlated with K6 score; weakness was correlated with the grip strength; resistance and slowness was correlated with gait speed; low physical activity and

inactivity was correlated with regular physical activity. Evidence for the item of shrinking in the FFP and ambulation and loss of weight in the FFPQ did not appear since no significant correlations were found between the change of these items and the changes of its corresponding measurements. Moreover, the change of total FFPQ score was correlated with the change of EEPA, daily percentage of MVPA, step, and K6 score, while the change of total FFP score was only correlated with the change of LPA.

Table 11. Characteristics of the Total Sample

Characteristics	Excluded, n=322 (Mean ± SD) or n (%)	Included, n=88 (Mean ± SD) or n (%)	*P* value
Age, year	71.4±3.2	71.0±3.4	0.37
Gender, men	165 (51.2)	44 (50.0)	0.84
BMI, kg/m^2	23.5±3.5	23.0±3.5	0.23
SMMI, kg/m^2	7.08±1.21	6.92±1.02	0.28
Grip strength, kg	27.1±8.1	28.3±7.9	0.22
5-time chair sit-to-stand, reps/second	1.96±0.65	1.90±0.64	0.44
Maximum gait speed, m/second	0.57±0.11	0.56±0.11	0.18
Normal gait speed, m/second	0.76±0.16	0.74±0.16	0.46
One-leg standing, second	69.9±45.6	75.9±42.7	0.27
EEPA, kcal/kg/hour	0.66±0.22	0.65±0.18	0.83
Daily percentage of TST	54.5±14.2	56.0±12.7	0.37
Daily percentage of LPA	39.7±11.6	38.7±11.0	0.46
Daily percentage of MVPA	5.78±4.77	5.28±3.87	0.37
Step, steps/hour	379.3±240.0	360.9±210.8	0.52
K6 score, point	4.11±3.37	5.56±3.86	0.001

SD, Standard Deviation; BMI, Body Mass Index; SMMI, Skeletal Muscle Mass Index; EEPA, Energy Expenditure of Physical Activity; TST, Total Sedentary Time; LPA, Light Physical Activity; MVPA, Moderate-to-Vigorous Physical Activity; K6, Kessler 6-item Psychological Distress Scale.

Table 12. Comparisons of Measurements in Paired t-Test Pre- and Post-Intervention

Characteristics	Pre-intervention (Mean ± SD)	Post-intervention (Mean ± SD)	Change (95% CI)	*P* value
Frailty				
Total score FFP	1.30±0.51	0.61±0.76	-0.68 (-0.83, -0.54)	<0.001
FFPQ	1.58±0.74	0.85±0.92	-0.73 (-0.95, -0.51)	<0.001
Exhaustion/Fatigue, score	0.47±0.50	0.11±0.32	-0.35 (-0.47, -0.23)	<0.001
Weakness, score	0.25±0.44	0.25±0.44	0.00 (-0.08, 0.08)	1.00
Resistance, score	0.47±0.50	0.33±0.47	-0.14 (-0.24, -0.03)	0.010
Slowness, score	0.10±0.30	0.00±0.00	-0. 10 (-0.17, -0.04)	0.002
Ambulation, score	0.10±0.30	0.08±0.27	-0.02 (-0.10, 0.06)	0.57
Low physical activity, score	0.24±0.43	0.14±0.35	-0.10 (-0.19, -0.01)	0.028
Inactivity, score	0.31±0.46	0.20±0.41	-0.10 (-0.23, 0.03)	0.13
Shrinking/Loss of weight, score	0.24±0.43	0.13±0.33	-0.11 (-0.22, -0.01)	0.041
Body composition				
BMI, kg/m^2	23.0±3.5	23.2±3.4	0.24 (0.07, 0.42)	0.007
SMMI, kg/m^2	6.92±1.02	6.96±1.00	0.04 (-0.03, 0.11)	0.22
Physical function				
Grip strength, kg	28.3±7.9	28.3±7.8	0.01 (-0.51, 0.52)	0.98
5-time chair sit-to-stand, reps/second	1.90±0.64	1.43±0.37	-0.47 (-0.58, -0.37)	<0.001
Maximum gait speed, m/second	0.56±0.11	0.55±0.09	-0.04 (-0.05, -0.02)	<0.001
Normal gait speed, m/second	0.74±0.16	0.68±0.11	-0.06 (-0.10, -0.03)	<0.001
One-leg standing, second	75.9±42.7	83.2±43.6	7.31 (0.42, 14.19)	0.038
Regular physical activity				
EEPA, kcal/kg/hour	0.65±0.18	0.67±0.18	0.02 (-0.01, 0.05)	0.15
Daily percentage of TST	56.0±12.7	55.4±11.2	-0.62 (-2.37, 1.13)	0.48
Daily percentage of LPA	38.7±11.0	39.0±10.0	0.31 (-1.28, 1.89)	0.70
Daily percentage of MVPA	5.28±3.87	5.59±4.30	0.31 (-0.36, 0.99)	0.36
Step, steps/hour	360.9±210.8	423.4±265.1	62.5 (22.9, 102.1)	0.002
Depression				
K6 score, point	5.56±3.86	4.47±3.14	-1.10 (-1.80, -0.38)	0.003

SD, Standard Deviation; CI, Confidence Interval; FFP, Fried Frailty Phenotype; FFPQ, Fried Frailty Phenotype Questionnaire; BMI, Body Mass Index; SMMI, Skeletal Muscle Mass Index; K6, Kessler 6-item Psychological Distress Scale; EEPA, Energy Expenditure of Physical Activity; TST, Total Sedentary Time; LPA, Light Physical Activity; MVPA, Moderate-to-Vigorous Physical Activity.

Table 13. Agreement of Using the FFP and FFPQ to Assess the Effect of Intervention

	FFP					
	Decline	Maintain	Improvement	Total	Spearman rho	Kappa
FFPQ						
Decline	2	1	2	5		
Maintain	3	14	7	24	0.42*	0.35*
Improvement	1	15	43	59		
Total	6	30	52	88		

FFP, Fried Frailty Phenotype; FFPQ, Fried Frailty Phenotype Questionnaire. *P<0.001.

Table 14. Correlations between the Change of Each Item and Outcome Measurements

Mearsurements	Total score		Exhaustion/ Fatigue	Weakness	Resistance	Slowness	Ambulation	Low physical activity	Inactivity	Shrinking/ Loss of Weight
	FFP	FFPQ								
BMI	-0.04	0.17	0.12	-0.29**	0.04	-0.01	0.04	0.19	0.14	-0.12
SMMI	-0.04	0.05	0.12	-0.10	0.02	0.17	0.08	-0.03	0.01	-0.05
Grip strength	-0.17	0.02	0.01	-0.48**	-0.16	-0.07	0.11	0.04	-0.01	0.07
5-time chair sit-to-stand	-0.07	0.05	0.02	-0.01	0.07	0.16	0.03	0.04	0.11	-0.05
Maximum gait speed	-0.21	0.08	-0.01	0.14	0.23*	0.32**	0.17	-0.10	-0.03	-0.001
Nonmal gait speed	-0.12	0.14	0.03	-0.04	0.19	0.30**	0.10	-0.16	0.05	0.03
One-leg standing	0.01	-0.06	-0.07	-0.03	-0.14	0.04	-0.05	-0.13	0.01	0.10
EEPA	-0.13	-0.29**	0.001	0.10	0.17	0.01	-0.14	-0.46**	-0.23*	0.08
Daily persentage of TST	0.18	0.17	-0.02	-0.05	0.07	-0.01	0.10	0.42**	0.16	-0.04
Daily persentage of LPA	-0.22*	-0.16	0.01	0.01	-0.04	-0.03	-0.13	-0.30**	-0.07	-0.04
Daily persentage of MVPA	-0.10	-0.31**	-0.01	0.04	-0.17	0.04	-0.07	-0.41**	-0.33**	0.08
Step	-0.11	0.22*	-0.04	0.05	-0.15	-0.02	-0.11	-0.44**	-0.22*	0.18
K6 score	0.19	0.23*	0.46**	-0.15	0.10	-0.04	-0.03	0.05	-0.01	-0.11

BMI, Body Mass Index; SMMI, Skeletal Muscle Mass Index; K6, Kessler 6-item Psychological Distress Scale; EEPA, Energy Expenditure of Physical Activity; TST, Total Sedentary Time; LPA, Light Physical Activity; MVPA, Moderate-to-Vigorous Physical Activity.*P<0.05, **P<0.01

4. Discussion

To the best of our knowledge, this is the first study that has evaluated the ability of the FFPQ as an instrument to assess the effect of a frailty intervention in Japanese community-dwelling older adults. In the present study, we found that a 6-month multicomponent exercise intervention program had an improved effect on frailty status defined by both FFP and FFPQ. Moreover, a fair agreement of the intervention effect was found between the two instruments indicated the potential ability of the FFPQ in assessing the effect of a frailty intervention. These findings suggest that the implementation of the FFPQ as an assessment instrument is feasible in a resource-limited setting when the FFP cannot be evaluated.

Previous studies showed that a single intervention such as nutritional supplementation (Buigues et al., 2016, Kim et al., 2015) and reduce polypharmacy (Potter et al., 2016) could not significantly improve or reverse the frailty status. However, exercise offers an effective model of a single intervention in frailty with multisystem benefits. Our results showed that a 6-month exercise intervention decreased the total score of both instruments and the frailty status of 49 for the FFP and 36 for the FFPQ was reversed from pre-frailty or frailty to robust. These findings coincide with those published by Kim et al., Ng et al., and Tarazona et al., in which a reduction of frailty prevalence was found after a single exercise intervention although

the exercise program was different (Kim et al., 2015, Ng et al., 2015, Tarazona-Santabalbina et al., 2016). The mechanism resulting in this phenomenon might be because exercise simultaneously up-regulates many systems that mutually regulate each other in combination make the whole organism could be returned to a higher functional level. Moreover, a fair agreement (kappa=0.35) of the exercise intervention effect was found between the FFP and FFPQ indicated the potential ability of the FFPQ in assessing the effect of a frailty intervention. Interestingly, the change of total FFPQ score was correlated with the change of EEPA, daily percentage of MVPA, step, and K6 score, while the change of total FFP score was only correlated with the change of LPA. The reason for causing these results is unclear and further research is still necessary.

In contrast with the similar effects of exercise intervention on the frailty status defined by both instruments, the effects on the components of the FFP or FFPQ definition must be further considered. In the present study, two self-reported items of exhaustion and shrinking in the FFP was the same as the item of fatigue and loss of weight in the FFPQ. As for the exhaustion/fatigue, our results showed that exercise intervention resulted in a significant reduction in the score of these items might be caused by the improvement of the depression (K6 score). Moreover, a significant correlation was also found between the change of exhaustion/fatigue score and the

change of the K6 score. These results were consistent with a previous study, in which a reduction in the Yesavage Geriatric Depression Index was found after 6-month exercise intervention (Tarazona-Santabalbina et al., 2016), and indicated that exhaustion/fatigue can be appropriately used in evaluating the effects of an exercise intervention on frailty status. Although shrinking/loss of weight is one criterion included in the definition of frailty based on the FFP and FFPQ, it was considered not appropriate in evaluating the effects of intervention in a previous study (Kim et al., 2015). In the present study, our results found an increase in the BMI, however, no significant correlations were found between the change of shrinking/loss of weight and the change of BMI or SMMI which confirmed the finding from the previous study.

Three components of the FFP definition including weakness, slowness, and low physical activity are performance-based, while the self-reported components of resistance, ambulation, and inactivity in the FFPQ are corresponding one-to-one to those in the FFP, respectively. It is no doubt that the item of weakness, slowness, and low physical activity in the FFP could be used to assess the effect of intervention since these items are all based on objective measurements and the change of each item showed the highest correlation with the changes of its corresponding measurements. Despite exercise intervention was not improved the score of weakness, as well as the

performance of the grip strength in the present study were consistent with previous study (Haider et al., 2017, Kim et al., 2015, Tieland et al., 2012), it does not mean exercise is not appropriate to use for improving muscle strength. The reason causing this in the present study might be because of the content of the exercise program. The "Itoshima Frail Preventive Gymnastics" mainly focuses on the lower body strength while grip strength is a measure of upper body strength. As for the items in the FFPQ, resistance was used to evaluate the lower body strength by participants' report on his/her capacity to climb stairs without using handrail or wall for support and ambulation were used to evaluate aerobic ability by participants' report on his/her capacity to walk 1 km without resting. Our results were as expected that the score change of the resistance was not correlated with the change of grip strength, but correlated with the change of maximum gait speed demonstrated its potential ability in assessing the effect of an intervention. However, no significant correlations were found between the change of ambulation and gait speed, as well as other measurements, indicated that this item was not appropriate in evaluating the effect of intervention. Although the exercise intervention in the present study did not improve the regular physical activity, the results showed that the change of inactivity was correlated with the change of EEPA, daily percentage of MVPA, and step demonstrated that this item is good enough to use as an assessment component on the

effect of an intervention. As a rapid assessment instrument, our results suggesting the FFPQ can be adopted in a large-scale setting or a resource-limited setting when the FFP cannot be evaluated, however, an elementary but important point is that the FFPQ cannot be expected to replace the FFP according to the results.

There are some limitations to this study. One main limitation was the design of this study. A number of threats such as attrition, un-blinded assessment, maturation, history, test effects, and regression effects cannot be controlled to the single group design maybe weaken the causal interpretation. Briefly, because random allocation was not used, the extent to which the differences might be caused by history, maturation, test or the regression artifact.

5. Conclusions

The FFPQ could be used as a rapid instrument to assess the effect of an exercise intervention on frailty in Japanese community-dwelling older adults.

Chapter 5. Overall discussion and conclusion

The primary purposes of this doctoral thesis were to develop and evaluate the reliability and validity of the Japanese FRAIL scale (FRAIL-J) and Fried Frailty Phenotype Questionnaire (FFPQ), and to explore modifiable lifestyle factors either causing or protecting against frailty defined both questionnaires which might inform future feasible approaches to managing frailty in Japanese community-dwelling older adults. Accordingly, the present thesis had three objectives as follows: 1) to develop a Japanese FRAIL scale and tried to modify it to make the FRAIL scale more close to the Fried Frailty Phenotype (FFP), then to evaluate the reliability and validity of both questionnaire (Study 1); 2) to investigate the association between lifestyle factors, particularly the objectively daily physical activity, and frailty defined by the FRAIL scale (Study 2); 3) to examine whether the FRAIL scale can be used as a frailty assessment instrument (Study 3).

In the first study, we developed a FRAIL-J and an FFPQ and evaluated the reliability and validity of both questionnaires in Japanese community-dwelling older adults. Overall, the results of this study showed that both questionnaires had low internal consistency, good test-retest reliability, acceptable construct validity, satisfactory diagnostic accuracy, and concurrent validity. In addition, a 2-point cut-off of both questionnaires or a 3-point cut-off of the FFPQ can be used as the first step for frailty screening in Japanese community-dwelling older adults.

The second study demonstrated that neither the sedentary behavior (SB) patterns nor sporadic moderate-to-vigorous physical activity (MVPA) was associated with pre-frailty or frailty defined by both questionnaires. Higher levels of total MVPA time and steps were not associated with pre-frailty but associated with frailty defined by both questionnaires. In addition, a significant association between bouted MVPA and frailty defined by the FRAIL-J was observed. Moreover, the 43.25 or 51.63 min/day of total MVPA, 9.13 min/day of bouted MVPA, and 3841 or 3702 steps/day of daily step were suggested as the optimal cut-off value to discriminate between frailty and non-frailty for the FRAIL-J and FFPQ, respectively. The main findings in this study provide evidence concerning how objective physical activity (PA) patterns are associated with frailty which might inform future feasible approaches to managing frailty in older Japanese adults.

In the third study, we found that a 6-month multicomponent exercise intervention program had an improved effect on frailty status defined by both FFP and FFPQ. Moreover, a fair agreement of the intervention effect was found between the two instruments indicated the potential ability of the FFPQ in assessing the effect of a frailty intervention. However, the item of ambulation and loss of weight in the FFPQ might not be appropriate in evaluating the effect of an exercise intervention. These findings suggest that the implementation of the FFPQ as an assessment instrument is

feasible in a large-scale setting or a resource-limited setting when the FFP cannot be evaluated, while an elementary but important point is that the FFPQ cannot be expected to replace the FFP.

To sum up, findings from this thesis have several public health implications. For now, although no gold standard frailty instrument exists, the FRAIL-J or its modified version FFPQ can be considered a viable alternative in screening frailty in Japan. Compare to the more complex frailty instruments such as the FFP or Frailty Index (FI) that must evaluate some objective measurements, the FRAIL-J and FFPQ not only simple, time-saving, and self-reported but also have satisfactory reliability and validity make it can be used in a large-scale setting or a resource-limited setting at a frequent interval, for example, a nationwide survey of frailty once a year. This is very meaningful to the public health which makes the policymaker or healthcare expert can effectively formulate policies or guidelines to manage the frailty nationwide. In addition, findings from the study 2 showed that although some inconsistent characteristics of frailty status screened by both questionnaires still existed, irrespective of whether FRAIL-J or FFPQ was used to screen frailty status, participants with frailty showed lower MoCA score, higher PSQI score, shorter total MVPA time and bouted MVPA, lower daily steps, and have a higher ratio of polypharmacy. Physical activity is considered as an effective model of a single

intervention in frailty with multisystem benefits. Therefore, among these causing/protecting factors, we further analyzed the factors of objective daily physical activity. Our results demonstrated that lower amounts of bouted MVPA (10 min per day) or steps (4000 steps per day) may be achievable initial targets in older adults for frailty management. These interesting findings point out a potential intervention method that combines bouted MVPA and daily steps together. For example, do a 10 min walk inside or outside with a cadence of at least 100 steps per min every day may be a simple but effective way to manage frailty. However, this value should be further confirmed among older adults in future intervention studies before these observations can be translated into public health guidelines. In view of the findings of studies 1 and 2, despite both questionnaires had similar internal consistency, test-retest reliability, construct and concurrent validity, diagnostic accuracy, and causing/protecting factors, comparatively speaking, the FFPQ was more close to the FFP (instead of illness using inactivity) and more flexible (2 or 3 points as the cut-off) using in the community-dwelling older adults. As professional and structural deficiencies in the health care system in the developing nations which also face the aging, it is not easy for the older adults to know whether they have had several diseases will also limit its part feasibility. Thus, compared to the FRAIL-J, the FFPQ could potentially be adopted by developing countries having professional and structural deficiencies in the health care

system. Moreover, as for the ability of assessing the effect of an exercise intervention on frailty, the item of illness in the FRAIL-J is also inappropriate because a past illness cannot be reversed. Therefore, in study 3, only the FFPQ was selected to evaluate whether it could be used as an instrument to assess the effect of an exercise intervention on frailty in Japanese community-dwelling older adults. The heartening findings showed that a fair agreement of the intervention effect was found between the FFP and FFPQ indicated the potential ability of the FFPQ in assessing the effect of a frailty exercise intervention.

Despite the implications mentioned above, this doctoral thesis also has several limitations worth noting. The main limitation to the studies 1 and 2 was the response bias which relates to the generalizability of the present findings. Participants in this study population were individuals 65 - 75 years old from just one southwest city in Japan and therefore it was not representative of the older Japanese population. In addition, the response rate was relatively low which could cause bias in interpreting the results since the participants that self-selected to participate in the study may be different from those who did not. Moreover, the cross-sectional design of the two studies precludes the ability to examine the causal inferences. Further nationwide prospective cohort study should be needed to examine the predictive ability of adverse outcomes using both FRAIL-J and FFPQ. The limitation to the study 3 was the

research design. Because random allocation was not used in study 3, the extent to which the differences might be caused by history, maturation, test or the regression artifact. Further randomized controlled trial study should be needed to confirm these findings.

In conclusion, this doctoral thesis reveals that the FRAIL-J and its modified version FFPQ have good test-retest reliability, acceptable construct and concurrent validity, and satisfactory diagnostic accuracy. Meanwhile, participants with frailty screened by both questionnaires showed similar causing/protecting factors. These findings make both questionnaires can be considered a viable alternative in frailty management. Moreover, the FFPQ was closer to the FFP and more flexible may be adopted by developing countries having professional and structural deficiencies in the health care system. More importantly, the heartening findings showed that the FFPQ can also use as an instrument in evaluating the effect of a frailty exercise intervention. To sum up the above findings, the application of the FFPQ in Japanese community healthcare can be systemized as following (Figure 7): first, the FFPQ will be used to screen the frailty status by mail or telephone among community-dwelling older adults aged 65 - 75 years older; second, older adults with pre-frailty or frailty will be introduced to participate in an exercise intervention class that uses the "Itoshima Frail Preventive Gymnastics" as the main course; third, after a period of intervention (e.g. 6 months),

the FFPQ will be used to assess the frailty status once again among these older adults who participate in the intervention class. Older adults still with pre-frailty or frailty can continue to take part in intervention class, while older adults without pre-frailty or frailty can select other daily living support services.

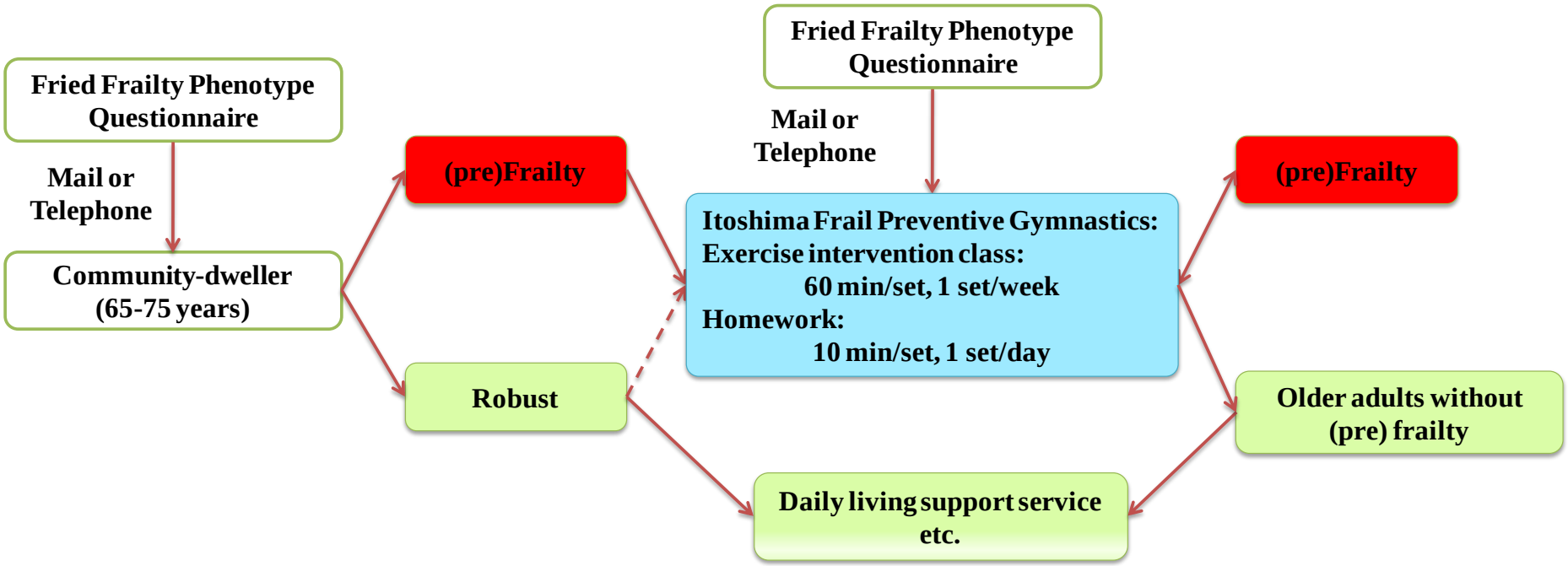

Figure 7. The application of the Fried Frailty Phenotype Questionnaire in the healthcare system

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