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Title page

Extracellular-to-intracellular water ratios are associated with functional disability levels in patients with knee osteoarthritis: Results from the Nagahama Study

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Abstract

Introduction/objectives: To test the hypothesis that greater extracellular-to-intracellular water (ECW/ICW) ratios in lower-limb muscles are associated with worsened functional abilities in patients with knee osteoarthritis (OA).

Methods: We analyzed data from 787 participants (82.2% female; mean age, 69.6 ± 5.3 years) from the Nagahama Prospective Cohort who were ≥60 years old and had radiographically confirmed bilateral knee OA. The Knee Scoring System (KSS) was used to assess functional abilities. Lower-limb ECW/ICW ratios and skeletal mass index values were determined with multi-frequency bioelectrical impedance analysis (BIA). Multiple linear regression analysis was used to test for associations between ECW/ICW ratios and functional abilities. Subgroup analyses based on OA severities and symptomaticity were also conducted.

Results: Increased ECW/ICW ratios were associated with a 4.38-point decrease in the KSS function scores (95% confidence interval [CI], 3.15–5.62 points) after adjusting for covariates. This association varied according to the degree of knee symptoms, especially in individuals with radiologically mild OA. ECW/ICW ratios in individuals with asymptomatic mild OA were associated with a 2.14-point decrease in the KSS function score (95% CI, 0.32–3.96 points), whereas those in individuals with severe symptomatic mild OA were associated with a 6.16-point decrease (95% CI, 2.13–10.19 points).

Conclusions: Our findings indicate that higher ECW/ICW ratios are associated with greater functional disability in patients with knee OA. Therefore, ECW/ICW ratio measurements with multi-frequency BIA can serve as valuable indicators for functional disability in patients with knee OA.

Key Points

- Higher extracellular-to-intracellular water (ECW/ICW) ratios are associated with greater functional disability levels in patients with knee osteoarthritis (OA).
- ECW/ICW ratios are useful clinical signs as a biomarker for poor functional abilities in patients with knee OA.

Keywords

Knee osteoarthritis, functional disability, muscle quality, extracellular-to-intracellular water ratio, bioelectrical impedance analysis

Declarations

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Conflicts of Interest:

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethics approval:

All study procedures were approved by the Ethics Committee of the Kyoto University Graduate School of Medicine and the Nagahama Municipal Review Board (G278) and were conducted in accordance with the principles of the Declaration of Helsinki.

Consent to participate and consent for publication:

Written informed consent for the use of data was obtained from all participants in the Nagahama Study.

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Authors' contributions:

All authors have made substantial contributions to (1) the conception and design of the study; (2) revising it critically for important intellectual content; and (3) final approval of the version to be submitted. The specific contributions of each author are as follows:

(1) Analysis and interpretation of the data: MT, TI, TK, and NI.

(2) Drafting of the article: MT, TI, TK, and NI.

(3) Statistical expertise: MT and TK.

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Text

Introduction

Dysfunction in thigh muscles is an established risk factor for incident knee osteoarthritis (OA) and the loss of functional abilities [1-3]. However, decreased thigh muscle mass cannot fully explain the muscle weakness observed in patients with knee OA, so researchers have suggested that high levels of muscular fat infiltration, which indicate poor muscle quality, accompany muscle dysfunction in such patients [4,5]. Therefore, examining local measures of muscle composition may elucidate the causes of functional disability in patients with knee OA.

A recent meta-analysis [6] reported that thigh muscle fat infiltration levels are higher in patients with knee OA than in healthy controls. Furthermore, models with adjustments for body mass index (BMI) values show that patients with knee OA have elevated levels of skeletal adipose tissue within the quadriceps muscle [7]. Interestingly, lower physical functionality in patients with knee OA are associated with higher intramuscular fat fractions but not with muscle size [7]. Additionally, previous studies [8,9] have reported that greater fat infiltration levels are associated with OA progression and knee pain. Therefore, greater fat infiltration levels may worsen mobility and the ability to perform activities of daily living, and knee OA severities may influence the association between knee function and muscle quality.

Multi-frequency bioelectrical impedance analysis (BIA) is a convenient, affordable, and noninvasive method for measuring skeletal muscle mass and adipose tissue levels within localized regions. Skeletal muscle tissue contains abundant water, and multi-frequency BIA can separately evaluate intracellular water (ICW) and extracellular water (ECW) [10,11]. ICW generally reflects muscle cell mass, and ECW reflects adipose tissue and interstitial fluid in the extracellular space [12]. Higher ECW/ICW ratios are indicative of greater levels of noncontractile tissue relative to skeletal muscle and are therefore biomarkers for loss of muscle quality [13]. Higher ECW/ICW ratios in lower-extremity muscles are associated with physical impairments independently of muscle mass, age, sex, and BMI [13]. However, no previous study has investigated the association between ECW/ICW ratios and functional abilities in patients with knee OA. It is also unknown whether this potential association is affected by the radiological grade and/or degree of knee pain.

The purpose of this study was to examine the associations between ECW/ICW ratios and functional abilities in patients with knee OA. We hypothesized that greater ECW/ICW ratios would be associated with worsened functional abilities in patients with knee OA. We also hypothesized that such associations would be particularly strong in patients with severe OA and those experiencing symptoms of knee pain or stiffness.

Materials and Methods

Study participants and selection

This cross-sectional study was conducted with participants from the Nagahama Prospective Cohort for Comprehensive Human Bioscience (herein referred to as the Nagahama Study). The Nagahama Study's participants were recruited between 2013 and 2016 from the general population of Nagahama City, a city with 125,000 inhabitants located in a predominantly rural area of the Shiga Prefecture of central Japan. In total, 9,850 individuals aged 35–81 years who lived independently in the community were enrolled. Of these individuals, 4,990 were aged ≥60 years, underwent body composition analysis, and completed a questionnaire about their habits in daily life, and 3,270 of those individuals underwent optional knee X-rays. We further restricted our sample to 850 participants with radiographically confirmed bilateral knee OA and then excluded 63 individuals with any of the following comorbidities: rheumatoid arthritis, central or peripheral nervous system impairments, chronic obstructive pulmonary disease, or chronic kidney disease necessitating dialysis. Ultimately, 787 individuals were included in our analyses (Figure 1).

All study procedures were approved by the Ethics Committee of the Kyoto University Graduate School of Medicine and the Nagahama Municipal Review Board (G278) and were conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent for the use of data was obtained from all participants in the Nagahama Study.

Assessments of physical characteristics, clinical features, and exercise habits

Each individual's height and weight were measured to the nearest 0.1 cm and 0.1 kg, respectively, and BMI values (in kg/m^2) were calculated as weight divided by height squared. The presence of diabetes or osteoporosis was detected by reviewing the cohort data. The participants reported their exercise behaviors and whether they experienced back pain on a questionnaire concerning activities of daily living. An exercise habit was defined as engaging in moderate-intensity physical activity for >30 minutes twice a week for at least a year.

Definition of radiographically confirmed knee OA

For bilateral X-ray knee assessments, anteroposterior weight-bearing views were obtained while participants kept both knees fully extended. Two experienced orthopedists who were blinded to clinical data evaluated the radiographic images according to the Kellgren-Lawrence (KL) grading system, with radiographically confirmed knee OA being defined as KL grades ≥2 for both knees [14]. For the present study, we defined mild knee OA as the presence of KL grades of 2 in both knees and moderate to severe knee OA (greater OA severities) as the presence of KL grade ≥3 in one or both knees.

Quantification of knee function and knee impairments

The Knee Society's Knee Scoring System (KSS), a standard measure of knee function and knee impairments, was used in the present study. The KSS is a self-administered assessment tool that reflects physical function and radiographically determines knee OA grades in the general Japanese population [15]. For the present analyses, we focused on two KSS categories: the functional activities category and the symptoms category.

The functional activities category of the KSS was chosen to measure the degree of disability in performing daily activities. This category is divided into four components: walking and standing (30 points), standard activities (30 points), advanced activities (25 points), and discretionary activities (15 points). The maximum possible functional activities score is 100 points, and higher scores represent better physical function levels.

The symptom category of the KSS is based on three components: the degree of knee pain during walking, the degree of knee pain while traveling up and down stairs, and knee stiffness. The scores range from 25 (i.e., no pain or stiffness) to 0 (i.e., the worst possible pain and stiffness). For this study, we categorized patients into groups based on three quantiles of the KSS symptom score as follows: asymptomatic: KSS symptom score $\geq$23, moderate: KSS symptom score $\geq$18, and severe: KSS symptom score $<$18.

Quantification of lower-limb ECW/ICW ratios and skeletal muscle mass index values

ECW/ICW ratios and skeletal muscle mass index (SMI) values in the lower limbs were assessed with a multi-frequency BIA device (InBody 430; InBody Co., Seoul, Republic of Korea) that featured an eight-polar tactile-electrode impedance meter. Bioelectrical impedances were obtained in each leg at frequencies of 5 and 250 kHz and an alternating current of 250 A. The impedance measurements at 5 kHz (Z_5) mainly reflected ECW, and the impedance measurements at 250 kHz (Z_{250}) reflected ICW. In accordance with the protocols of previous studies [16,17], the impedance for the ECW (in cm^2/Ω) was calculated as (body height)$^2/Z_5$. The impedance of the ICW compartment (Z_{250-5}) was calculated as $1/[(1/Z_{250}) - (1/Z_5)]$, and the impedance for the ICW (in cm^2/Ω) was calculated as (body height)$^2/(Z_{250-5})$. For each individual, the ECW/ICW ratio in each leg was calculated as Z_5/Z_{250-5}, and the average ratio for both legs was then calculated. The summed muscle mass of both legs was divided by the square of the individual's height to yield a lower-limb SMI value (in kg/m^2) [18].

Statistical analysis

For descriptive analyses, continuous variables are expressed as means ± standard deviations (SDs), and categorical variables are expressed as counts and percentages.

For our primary analysis of whether ECW/ICW ratios were associated with functional abilities, we performed a multiple linear regression analysis with ECW/ICW ratios as the independent variable and KSS function scores as the dependent variable. A multiple linear regression analysis was conducted with adjustments for lower-limb SMI values, age, sex, BMI values, radiographically measured OA severities, symptomaticity, and the presence or absence of diabetes, osteoporosis, exercise habit, and back pain.

We also performed several secondary analyses. First, we repeated the primary analysis in each subgroup, separated by radiographically determined OA severity (i.e., mild or greater OA severities) and by three quantiles of the KSS symptom score (i.e., asymptomatic, moderate, or severe), with the resulting scheme including six subgroups. Second, we performed a multiple linear regression analysis with ECW/ICW ratios as the dependent variable to identify the variables associated with ECW/ICW ratios. All statistical analyses were performed with SPSS software version 25.0 (SPSS Japan Inc., Tokyo, Japan). The statistical significance threshold was set at $p < 0.05$.

Results

Of the 787 individuals in our sample, 82.2% were female. The mean age was 69.6 ± 5.3 years, and the mean BMI value was 23.4 ± 3.2 kg/m^2. The mean KSS function and symptoms scores were 82.3 ± 17.4 points and 19.0 ± 6.0 points, respectively. Table 1 shows the baseline characteristics of the individuals in our sample.

In the primary analysis, an increased ECW/ICW ratio was associated with a 4.38-point decrease in the KSS function score (95% confidence interval [CI], 3.15–5.62 points) after adjustments for covariates (Table 2). In subgroup analyses, the association varied according to the degree of knee symptoms, especially in individuals with mild OA (Table 3). For example, an increase in ECW/ICW ratio was associated with a 2.14-point decrease in the KSS function score (95% CI, 0.32–3.96 points) in individuals with asymptomatic mild OA but with a 6.16-point decrease (95% CI, 2.13–10.19 points) in those with severe symptomatic mild OA.

In exploratory analyses, greater lower-limb SMI values, higher BMI, and the presence of an exercise habit were associated with lower ECW/ICW ratios, and severe OA, worse KSS symptom scores, older, female sex, and the presence of osteoporosis were associated with greater ECW/ICW ratios (Table 4).

Discussion

The present study is the first to show that higher ECW/ICW ratios, which reflect greater noncontractile tissue masses within the skeletal muscles, are associated with worse KSS function scores in patients with knee OA. This association was particularly strong in individuals who were symptomatic and had greater OA severities. These results are consistent with our hypotheses.

Recently, Misra et al. [19] reported that body composition-based obesity and sarcopenic obesity, but not sarcopenia, are associated with knee OA, and an earlier study [20] reported that higher ratios of fat mass to muscle mass, as measured with BIA, are associated with symptomatic knee OA. These previous findings suggest that greater adipose tissue levels are associated with knee OA. Adiposity enhances the metabolic effect of adipose tissue products such as cytokines and adipokines, which regulate chondrocyte anabolism and thus play key roles in joint cartilage pathophysiology [21]. Furthermore, an association between adiposity and knee OA suggests that obesity increases mechanical stress across the knee joint and thus leads to cartilage damage [22]. However, there is no consensus regarding the association between high BMI values and functional disability [23-25]. This disagreement may arise from the fact that the BMI formula does not distinguish between fat mass and lean body mass. Our results indicate that higher ECW/ICW ratios, which indicate relative increase of adipose tissue to muscle mass, are associated with low KSS function scores in patients with knee OA.

The results of the primary analysis indicated that not only higher ECW/ICW ratios but also OA severities and symptomaticity were associated with worse KSS function scores. Furthermore, our findings in subgroup analyses suggested that the association between an increase in ECW/ICW ratio and functional ability was strong in individuals with more severe symptoms who had radiologically mild knee OA. Muscle inflammation and increased adipose tissue levels within the quadriceps muscle often accompany symptomatic knee OA and may contribute to physical dysfunction in patients [26,27]. A previous study [7] that used magnetic resonance imaging (MRI) to evaluate quadriceps muscle mass and muscular fat fractions in patients with knee OA reported that muscular fat fractions, but not muscle mass, are associated with pain and self-reported functional disability. This is consistent with our observation that lower muscle quality, as measured with multi-frequency BIA, is associated with self-reported disability. Thus, our results and those of other studies suggest that muscle quality is an important factor related to physical dysfunction, especially in patients with symptomatic severe knee OA.

The ECW/ICW ratio is a recognized biomarker for muscle quality because it is associated with muscle strength and physical function independent of age, BMI values, and SMI values in community-dwelling older adults [28]. Our results indicate that increased ECW/ICW ratios in patients with knee OA are associated with decreased lower-limb SMI values, worsened symptoms, and greater OA severities. Therefore, increased ECW/ICW ratios may be useful biomarkers for symptomaticity and poor functional abilities in patients with knee OA. Moreover, the results of exploratory analyses showed that advanced age, female sex, and the presence of osteoporosis were associated with greater ECW/ICW ratios. As the amount of physical activity is reduced in postmenopausal females with osteoporosis [29], the increased ECW/ICW ratios could be caused by inactivity. In fact, our results indicated that the presence of an exercise habit was associated with lower ECW/ICW ratios. Approaches to factors that are associated with ECW/ICW ratios may also be important for improving functional abilities in patients with knee OA.

Although multi-frequency BIA lacks the ability of MRI and computed tomography (CT) to differentiate individual thigh muscles, it is free of the major limitations of quantitative methods such as MRI, CT, and dual-energy X-ray absorptiometry (DXA), which include inconvenience, high costs, and radiation exposure. The lower-limb lean tissue mass measurements, obtained with the device used in the present study, correlate strongly with lower-limb muscle mass measurements obtained with DXA [30]. Multi-frequency BIA therefore shows great potential as a tool for future research into markers of muscle quality in patients with knee OA.

This study has some limitations. First, its cross-sectional design means that it could not determine whether increased ECW/ICW ratios cause dysfunction in patients with knee OA. Intramuscular fat content is a predictor of OA progression [8], so future studies should examine whether increased ECW/ICW ratios worsen functional disability in patients with knee OA. Second, our focus on Nagahama Study participants who opted for X-ray examinations is a possible source of selection bias. Indeed, when we compared the characteristics of our study population with those of Nagahama Study participants who did not opt for X-ray examinations, we found that the latter group had lower KSS function scores and higher ECW/ICW ratios (Supplementary Table). If many of the participants who did not undergo X-ray examinations had bilateral knee OA, then our analyses could have underestimated the strength of the association between functional disability and muscle quality. Finally, multi-frequency BIA with an eight-polar tactile electrode cannot differentiate the thigh from the shank. However, segmental-bioelectrical impedance spectroscopy (S-BIS) has recently been used for regionally specific muscle quality assessments [31-33]. Future studies should use longitudinal S-BIS assessments of muscle quality in the thigh to clarify how poor muscle quality influences functional disability in patients with knee OA.

In conclusion, higher ECW/ICW ratios are associated with greater functional disability levels in patients with knee OA, and the association is stronger in the patients with symptomatic OA and greater OA severities. Muscle quality assessments based on multi-frequency BIA measurements of ECW/ICW ratios are therefore more useful than muscle quantity assessments as a biomarker for poor functional abilities in patients with knee OA.

Conflicts of Interest:

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Table 1. Characteristics of the individuals with knee OA

Characteristic	Mean ± SD or n (%)
ECW/ICW ratio	5.2 ± 0.8
Lower-limb SMI, kg/m^2	2.4 ± 0.3
OA severity	
Mild; KL grades = 2 for both knees	539 (68.5%)
Moderate-severe; KL grade ≥3 in one or both knees	248 (31.5%)
Symptom severity	
Less: KSS symptom score ≥23	275 (34.9%)
Mild: KSS symptom score ≥18	264 (33.6%)
Severe: KSS symptom score <18	248 (31.5%)
Diabetes	79 (10.0%)
Osteoporosis	143 (18.2%)
Exercise Habit: >2 days/wk	328 (41.7%)
Back Pain	434 (55.1%)

Symptom severities were categorized into patient subgroups based on three quantiles of the KSS symptom score.

Abbreviations: ECW/ICW, extracellular-to-intracellular water; KSS, Knee Scoring System; OA, osteoarthritis; SD, standard deviation; SMI, skeletal muscle mass index

Table 2. Associations between study variables and KSS function scores

	Association with KSS function scores		
Variable	Regression coefficient	95% CI	*P* value
ECW/ICW ratio	-4.38	-5.62 to -3.15	<0.001
Lower-limb SMI, kg/m^2	2.29	-0.76 to 2.40	0.340
Greater OA severities	-2.14	-4.09 to -0.20	0.031
Symptom severities: Less	ref.		
Mild	-5.75	-7.85 to -3.65	<0.001
Severe	-19.90	-22.2 to -17.6	<0.001
Age, y	-0.40	-0.58 to -0.22	<0.001
Female sex	0.49	-2.66 to 3.64	0.760
BMI, kg/m^2	-1.17	-1.50 to -0.84	<0.001
Diabetes	-3.29	-5.98 to 0.43	0.022
Osteoporosis	-1.09	-3.40 to 1.22	0.355
Exercise habit	3.07	1.31 to 4.83	0.001
Back pain	-4.25	-6.07 to -2.43	<0.001

A multiple linear regression analysis was conducted with ECW/ICW ratios as the independent variable and KSS function scores as the dependent variable, with adjustments for lower-limb SMI values, age, sex, BMI values, OA severities (reference, mild OA), symptomaticity, and the presence or absence of diabetes, osteoporosis, an exercise habit, and back pain.

Abbreviations: BMI, body mass index; CI, confidence interval; ECW/ICW, extracellular-to-intracellular water; KSS, Knee Scoring System; OA, osteoarthritis; Ref, reference; SMI, skeletal muscle mass index

Table 3. Associations between ECW/ICW ratios and KSS function scores for subgroups defined by OA severities and symptomaticity

Category		n	Change in KSS function scores with ECW/ICW ratios		
OA severity	Symptom severity		Regression coefficient (B)	95% CI	*P* value
Mild OA	Asymptomatic	233	-2.14	-3.96 to -0.32	0.022
	Moderate	187	-3.86	-6.43 to -1.29	0.003
	Severe	119	-6.16	-10.19 to -2.13	0.003
Greater OA severities	Asymptomatic	42	-6.10	-9.94 to -2.26	0.003
	Moderate	77	-4.36	-9.04 to 0.32	0.067
	Severe	129	-5.36	-8.67 to -2.06	0.002

The secondary analysis was conducted in six subgroups, separated by radiographically determined OA severity (i.e., mild or greater OA severities) and by three quantiles of the KSS symptom score (i.e., asymptomatic, moderate, or severe). A multiple linear regression analysis was conducted with adjustments for lower-limb SMI values, age, sex, BMI values, radiographically measured OA severities, symptomaticity, and the presence or absence of diabetes, osteoporosis, an exercise habit, and back pain.

Regression coefficient represents changes in KSS function score (points) in each group.

Abbreviations: CI, confidence interval; ECW/ICW, extracellular-to-intracellular water; KSS, Knee Scoring System; OA, osteoarthritis

Table 4. Factors associated with ECW/ICW ratios

	Association with ECW/ICW ratios		
Variable	Regression coefficient	95% CI	*P* value
Lower-limb SMI (kg/m^2)	-0.42	-0.68 to -0.15	0.002
Greater OA severities	0.18	0.07 to 0.29	0.002
Symptom severities; asymptomatic	ref		
moderate	0.11	-0.10 to 0.23	0.072
severe	0.23	0.10 to 0.36	0.001
Age, y	0.04	0.03 to 0.05	<0.001
Female sex	0.37	0.19 to 0.55	<0.001
BMI, kg/m^2	-0.03	-0.05 to -0.01	0.006
Diabetes	0.12	-0.04 to 0.28	0.143
Osteoporosis	0.27	0.14 to 0.40	<0.001
Exercise habit	-0.16	-0.26 to -0.06	0.002
Back pain	0.02	-0.09 to 0.12	0.720

A multiple linear regression analysis was conducted with ECW/ICW ratios as the dependent variable to identify the variables associated with ECW/ICW ratios.

Abbreviations: BMI, body mass index; CI, confidence interval; ECW/ICW, extracellular-to-intracellular water; KSS, Knee Scoring System; OA, osteoarthritis; Ref, reference; SMI, skeletal muscle mass index

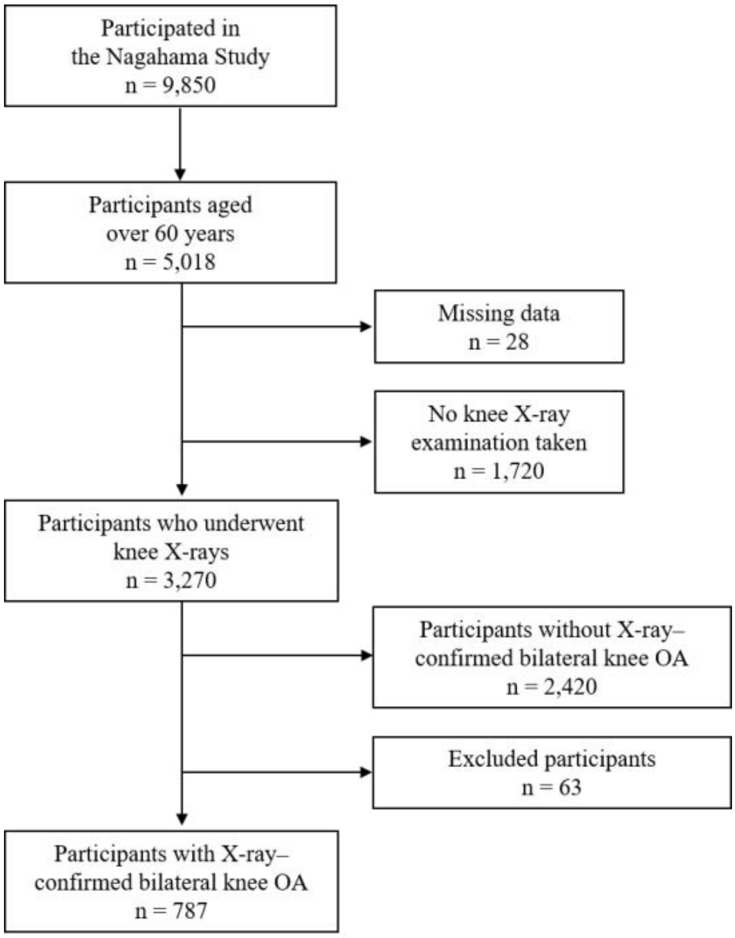

Fig. 1 Flowchart for selection of participants from the Nagahama Study

Abbreviation: OA, osteoarthritis