Examination of the body composition of patients with Werner syndrome using bioelectrical impedance analysis

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Running head: Body Composition of Werner Syndrome

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Abstract

Aim

This study performed anthropometric measurements for Werner syndrome (WS) using bioelectrical impedance analysis (BIA) and compared them with the Japanese reference data.

Methods

The analytical sample included nine WS participants (4 males, 5 females, 49.6 ± 9.3 years, SD). The height-corrected appendicular skeletal muscle mass index (SMI), upper- and lower-limb muscle mass index (USMI/LSMI) of WS patients were compared with Japanese reference data (40-79 years). The body mass index (BMI), SMI, height-corrected fat mass index (FMI), and fat-free mass index (FFMI) were compared with the reference data of Japanese older adults (65-94 years). The SMIs of WS were also compared with the diagnostic criteria for sarcopenia.

Results

The SMI and USMI/LSMI of all WS participants were lower than the Japanese reference data corresponding to gender and age, and the rate of decrease was more pronounced for USMI than for LSMI. The BMI, SMI, and FFMI for all the WS cases were lower than those for older Japanese, while the FMI was higher in males with WS but lower in females than the reference data of older Japanese. The SMI was below the cut-off value for the diagnosis of sarcopenia in all the patients with WS.

Conclusion

The SMI for WS is comparable to that for sarcopenia and significantly lower than that for healthy individuals of the same age and older adults. The USMI was significantly lower than LSMI in WS patients, and FMI was higher in male WS patients and lower in

females than in healthy older people.

Introduction

Werner syndrome (WS), an autosomal recessive disorder known as progeria, is characterized by various aging-related symptoms after puberty and the early onset of age-related disorders [1-3]. Approaches to controlling various aging-related symptoms of WS and a radical cure for WS have not yet been established. The average age of death of WS patients was previously reported to be within the 40s [1], but their life expectancy has increased recently [4], and some patients have been reported to survive for 70 or more years [5]. It has been reported that approximately 80% of patients with WS globally are in Japan; there are approximately 2000 WS patients in Japan [6]. According to the diagnostic criteria for WS reported by Japan in 2013, the symptomatology includes cataract (often bilateral), calcification of Achilles tendon, scleroderma-like skin, skin ulcer (especially sole and Achilles tendon), glucose tolerance disorder, and dyslipidemia and malignant tumors are likely to appear after the 20s [3].

The WS patients may experience changes in body features, such as skeletal muscle mass, due to accelerated aging [7]. Only one report using dual-energy X-ray absorption assay (DXA) and computed tomography (CT) has evaluated the body composition of multiple WS cases [8]. In addition to DXA and CT, there is an inexpensive and highly mobile bioelectrical impedance analysis (BIA) method for analyzing body composition, without radiation exposure, and it has become widespread recently. However, there are no studies on BIA of body composition for multiple WS patients. Furthermore, there is no report on the measurement of body fat for multiple WS cases and its comparison with Japanese reference data.

The purpose of this study was to investigate BIA for body composition analysis for patients with WS. (1) The appendicular skeletal muscle mass (MS) and bilateral

upper- and lower-limb muscle mass (USM, LMS) of multiple WS patients were compared with reference data for Japanese with various age groups matched for gender and age. (2) The MS, fat-free mass (FFM), and fat mass (FM) of the WS patients were compared with the reference data for community-dwelling older adults. (3) The SM of WS patients was compared with the cut-off value for sarcopenia diagnosis set by the Asian Working Group for Sarcopenia 2019 (AWGS 2019) [9].

Methods

1. WS patients participated in this study

The study included patients with WS who visited the geriatric outpatient clinic of Nagoya University Hospital from July 2014 to November 2018. Nine WS patients (4 males, 5 females, average age 49.6 ± 9.3 years, SD) diagnosed by a geriatric physician according to the diagnostic criteria of WS [3] were included in the present study.

This study was conducted according to the ethical principles of the Declaration of Helsinki and approved by the Clinical Research Review Committee of Nagoya University Hospital. The purpose and details of the study were explained to the participants verbally and in writing, and written informed consent was obtained from all participants before their inclusion in the study. The WS patients were registered with Nos. 1–9 in the order of consent.

2. Measurements

The data of the WS participants, including gender, age, presence or absence of foot ulcer, and blood test data such as serum albumin, HbA1c, and HOMA-R, which are calculated based on serum glucose and insulin concentration in the early morning, were obtained from the electronic medical records. The diabetes medications, blood test data,

height, weight, and body mass index (BMI), which is defined as weight (kg) divided by height (m) squared, from the period closest to the body composition analysis using BIA were used.

3. Body composition measurement

The body composition, including SM, USM, LSM, fat mass (FM), and fat-free mass (FFM) were measured using BIA (InBody®S10, InBody Japan, Tokyo), which uses a segmental multi-frequency approach (1, 5, 50, 250, 500, and 1,000 kHz). The InBody S10 is a device that can be used to take measurements in the supine, sitting, and standing postures. Assuming that WS patients have sole or Achilles tendon ulcers, it is difficult to maintain a standing posture for a long time. Therefore, in this study, the body composition of all participants was measured in the supine position.

The height-corrected body composition indices (SM index: SMI, USM index: USMI, LSM index: LSMI, FM index: FMI, FFM index: FFMI kg/m^2) were calculated by dividing SM, USM, LSM, FM, and FFM by the square of the height (m).

4. Physical performance and muscle power measurements

Grip strength and walking speed could not be measured accurately due to the deformed finger joints of the hands and intractable ulcers of the sole and Achilles tendon (Table); therefore, these measurements were not used in the present study.

5. Analysis

The body composition of WS participants was evaluated using the following three methods.

1) The SMI, USMI, and LSMI of the WS patients were compared with the Japanese reference data for various age groups. The reference data used were averages of age- and gender-matched SMI, USMI, and LSMI measured with BIA for a large healthy

Japanese cohort (male: n=16,379; female: n=21,660) aged 40-79 years [10]. By dividing the SMI, USMI, and LSMI of theWS participants by the average Japanese reference data corresponding to each gender and age group (40–44 years, 45–49 years, 50–54 years, 55–59 years, 60–64 years, 65–69 years, 70–75 years, and 74–79 years) and multiplying by 100, the %SMI, %USMI, and %LSMI were obtained. One 39-year-old female WS patient was compared with reference data for females 40-49 years.

2) The BMI, SMI, FMI, and FFMI of the WS patients were compared with the reference data of older people in Japan (65-94 years) [11]. The reference data used were age-group- (65-69 years, 70-74 years, 75-79 years, 80-84 years, and 85 years and over) and gender-specific mean BMI, SMI, FMI, and FFMI of community-independent older people aged 65 years and above (male: n=2,145, average age 72.9 years; female: n=2333, average age 72.6 years) [11].
3) The cut-off value of the SMI (7.0 kg /m^2 for males and 5.7 kg /m^2 for females) measured by BIA for the diagnosis of sarcopenia set by the Asian Working Group for Sarcopenia 2019 (AWGS 2019) [9] was compared with the SMI of the WS patients.

The Mann-Whitney U test (SPSS, version 28, IBM Corp, Armonk, NY, USA) was used to compare the two groups.

Results

Table shows the characteristics of the nine WS participants. The BMI was below 22.0 kg/m^2 for all the WS patients; it was significantly lower in women than in men ($p<0.05$). The serum albumin concentrations of the WS patients were 4.0 g/dl or higher, which was within the normal range. Of the nine WS participants, four had ulcers of the sole or Achilles tendon, four had finger joint deformities, and all had clinically diagnosed

diabetes mellitus or insulin resistance judged by HOMA-R.

Figure 1 shows the individual %SMI, %USMI, and %LSMI of the WS patients, which represent the percentages of the individual SMI, USMI, and LSMI age-matched with the Japanese age-group reference data (100%). The %SMI, %USMI, and %LSMI were less than 100% for all cases. In addition, %USMI was significantly lower than %LSMI ($p<0.001$), although there were no significant differences in %USMI and %LSMI between the male and female WS patients.

The BMI, SMI, FMI, and FFMI of the WS patients were compared with the reference data of the older Japanese (Fig. 2 and 3). All WS patients had lower BMI, SMI, and FFMI than the older adults. The SMI and FFMI of all the WS patients, both male and female, were lower than the average for community-dwelling older adults aged 85 and above. Compared with these reference data of Japanese older adults, female WS patients appeared to have lower BMI than their male counterparts (Fig.2A), and FMI was higher in three of the four males with WS (Fig.3B). On the other hand, all five WS female patients had lower FMI than the older adults.

The SMI of all the WS patients, both male and female, was below the cut-off values of 7.0 kg/m^2 for males and 5.7 kg/m^2 for females for the diagnosis of sarcopenia set by AWGS 2019 [9].

Discussion

In this study, we analyzed the body composition of Japanese patients with WS using BIA. The SMI was lower for WS patients than for healthy individuals of the same age group, as well as community-dwelling older people aged 65 and above, and it was reduced to sarcopenic levels according to the diagnostic criteria of AWGS 2019 [9]. A report

on body composition analysis using BIA by Yamada and Seino et al., which were used as reference data in the present study, revealed that SMI showed an age-dependent decrease [10,11]. As the average age of onset of aging-related symptoms in patients with WS is within their 20s [12], the skeletal muscle mass of WS patients may also begin to decline from a relatively young age.

Yamaga et al. performed body composition analysis for nine Japanese WS patients using DXA [8], and the SMIs of eight participants were less than the diagnostic cut-off for sarcopenia set by AWGS (male 7.0 kg /m^2, female 5.4 kg /m^2) [13]. This is consistent with the result of the body composition analysis using BIA for the present study. Neither our study nor the study of Yamaga et al. included WS patients in their twenties; however, the results of both studies suggest that WS patients aged around 40 have a decrease in SMI up to sarcopenic levels.

This study allowed the comparison of USMI and LSMI for patients with WS and the reference data. According to a report by Yamada et al., the USMI and LSMI for healthy Japanese decreased in an age-dependent manner, and the decrease was more remarkable in the lower limbs than in the upper limbs; the decrease in USMI in older adults was more pronounced in men than in women [10]. Although no gender differences in %USMI or %LSMI were observed for the WS patients in the present study, %USMI was significantly lower than %LSMI. Unlike healthy older adults, a lower USMI than LSMI may be among the physical characteristics of patients with WS. And its exact cause is unknown, but at least it may not be explained simply by the progression of aging phenomenon, since the age-related decrease in SMI was more pronounced in the LSMI in the Yamada et al. study [10].

Among the participants in this study, the No. 4 male, who carried the type 4

homozygous mutation (c.3139–1G>C), was very conscious of his health, routinely conducted resistance training involving the upper limbs at a fitness club, and had a relatively high %USMI. There is evidence for a positive and significant effect of resistance training on muscle mass, muscle strength, and physical performance in older adults [14,15]. Even in WS patients, resistance exercises involving the upper limbs may be associated with the prevention of skeletal muscle loss.

In this study, we also compared BMI, SMI, FFMI, and FMI of WS participants with reference data of independent older people in the community, and the WS patients had lower BMI, SMI, and FFMI than those in the community who were 85 years or older. It should be noted that the serum albumin concentrations in these WS participants were normal; therefore, the decline in these body composition indexes was not due to poor nutritional status. On the other hand, male WS patients tended to have higher FMI while their female counterparts tended to have lower FMI than community-dwelling older adults. In general, SMI and FFMI decreased and FMI increased with aging [10,11,16]. Similar changes were thought to occur in WS patients with accelerated aging. Male WS patients had higher FMIs as expected, but a new finding was that female patients with WS had lower FMIs than older adults in the community. The results showed that the BMI of female WS participants was lower than that of male participants, and it was also lower than that of independent older adults in the community. Since there was no gender difference in the other anthropometric indices, the main cause of lower BMI in females seemed to be a decrease in FMI. In a few reports on BIA for age-related changes in anthropometry, including old age, FM was higher in the young-old but lower in the old-old for both sexes than in adults [11,16]. Females with WS may be more aged than males. Yamaga et al. observed visceral fat accumulation as assessed by CT in female WS

patients (mean BMI similar to that of the female WS patients in our study), especially above the age of 50 years [8]. One of the limitations of our study was that we could not quantify the distribution of fat accumulation, so it is unclear whether visceral fat accumulation also existed in our WS patients.

It should be noted that in the study of 8 subjects for whom HOMA-R could be measured, SMI and FMI did not show a significant correlation with HOMA-R (data not shown). These results suggest that insulin resistance is not a major factor influencing SMI and FMI in our patients with WS. In any case, further research is needed to clarify the causes of gender differences in FMI in patients with WS. Looking at male WS patients, FMI was lower than the reference data of the older adults only for WS participant No. 4, who trained daily. From this observation, male patients with WS may prevent the accumulation of FM by appropriate exercises.

The limitations of this study are as follows. First, WS is a rare disease, and only nine patients participated in the study; therefore, the statistical analysis may not be optimal. Second, the reference data used in this study were the results of a survey by Yamada et al., who recruited participants by advertising in fitness and community centers [10]. The participants may have been highly conscious of health and may have had a better body composition than healthy people. Third, the distribution of fat mass (for example, quantification of subcutaneous and visceral fat) could not be measured in the present study. Finally, diabetes medications may affect skeletal muscle [17], but due to the small number of cases in this study, we were not able to evaluate the involvement of these medications in SMI.

In conclusion, BIA showed that the SMI of Japanese WS patients was lower than that of healthy subjects of the same age group, as well as that of independent older

adults in the community and that their SMI reduced to sarcopenic levels. In addition, WS patients showed a marked decrease in SMI in the upper limbs rather than in the lower limbs, and female WS patients had a lower FMI than community-dwelling older people unlike what is observed with normal age-related changes. The study showed that daily resistance exercise training may prevent a decrease in SM and an increase in FM, although is based on the experience of only one patient.

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Disclosure

The authors have no potential conflicts of interest to declare regarding this manuscript.

Figure 1.

Comparison of SMI (A), USMI (B), and LSMI (C) of individual WS participants with Japanese reference data for specific gender and age groups. The data (%SMI, %USMI, and %LSMI) show each index of individual WS participants as a percentage of the average value of the Japanese reference data for each gender and age group [10].

Figure 2.

Comparison of BMI (A) and SMI (B) for WS patients with the reference data of the older adults in Japan (65-94 years) [11]. The data show the BMI and SMI of individual WS participants by gender. The reference data used were the age-group- (65-69 years, 70-74

years, 75-79 years, 80-84 years, and 85 and over) and gender-specific means ± SD of BMI and SMI of community-dwelling older adults [11].

Figure 3

Comparison of FFMI (A) and FMI (B) of WS patients with the reference data of older adults in Japan (65-94 years). The data show the FFMI and FMI of individual WS participants by gender. The reference data used were the age-group- (65-69 years, 70-74 years, 75-79 years, 80-84 years, and 85 and over) and gender-specific means ± SD of FFMI and FMI of community-dwelling older adults [11].

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Table 1 Characteristics of participants

Registration number	1	2	3	4	5	6	7	8	9
Age(years)	70	51	49	43	48	43	39	46	57
Gender	male	male	female	male	female	male	female	female	female
Height (m)	1.52	1.57	1.53	1.51	1.47	1.63	1.48	1.58	1.53
Weight (kg)	44.0	51.0	40.5	48.0	39.0	51.5	34.0	42.4	39.2
BMI (kg/m^2)	19.0	20.7	17.3	21.1	18.0	19.4	15.5	16.9	16.7
Deformed finger joints	+	+	+	–	–	–	–	–	+
Foot ulcers	+	–	+	–	–	+	–	–	+
HbA1c(%)	9.9	7.3	6.8	5.9	6.5	7.3	5.7	N/A	7.6
HOMA-R	6.4	6.2	6.5	3.2	2.3	3.2	6.0	3.5	N/A
Diabetic medicine	SU, DPP4i	biguanide	TZD	N/A	N/A	N/A	N/A	biguanide	DPP4i, insulin
Alb(g/dl)	4.1	4.9	4.5	4.9	4.7	4.7	5.3	4.6	4.3
SM (kg)	9.7	10.8	10.9	14.3	9.1	14.5	8.1	11.5	9.9
SMI (kg/m^2)	4.19	4.39	4.64	6.28	4.19	5.47	3.68	4.58	4.19
USM (kg)	1.60	1.86	1.31	3.35	1.13	2.94	1.50	2.21	1.62
USMI (kg/m^2)	0.69	0.75	0.56	1.47	0.52	1.11	0.68	0.88	0.69
LSM (kg)	8.09	8.95	9.55	10.96	7.93	11.60	6.57	9.28	8.23
LSMI (kg/m^2)	3.50	3.63	4.08	4.81	3.67	4.36	3.00	3.70	3.50
FFM (kg)	25.6	25.4	26.3	35.7	24.5	33.6	24.1	27.7	26.3
FFMI (kg/m^2)	11.1	10.3	11.2	15.7	11.3	12.6	11.0	11.0	11.2
FM (kg)	18.4	25.6	14.2	12.3	14.5	17.9	9.9	14.7	12.9
FMI (kg/m^2)	7.96	10.39	6.07	5.39	6.71	6.73	4.52	5.86	5.48

BMI: body mass index, HOMA-R: homeostasis model assessment-(insulin) resistance, Alb: albumin, FM: fat mass, FMI: fat mass index, FFM: fat-free mass, FFMI: fat-free mass index, SM: appendicular skeletal muscle mass, SMI: skeletal muscle mass index, N/A: not applicable, USM: upper limbs muscle mass, USMI: upper limbs muscle mass index, LSM: lower limbs muscle mass, LSMI: lower limbs muscle mass index, +: presence, -: absence, SU: sulfonylurea, DPP4i: dipeptidyl peptidase-4 inhibitor, TZD: thiazolidine derivative.

Fig.1

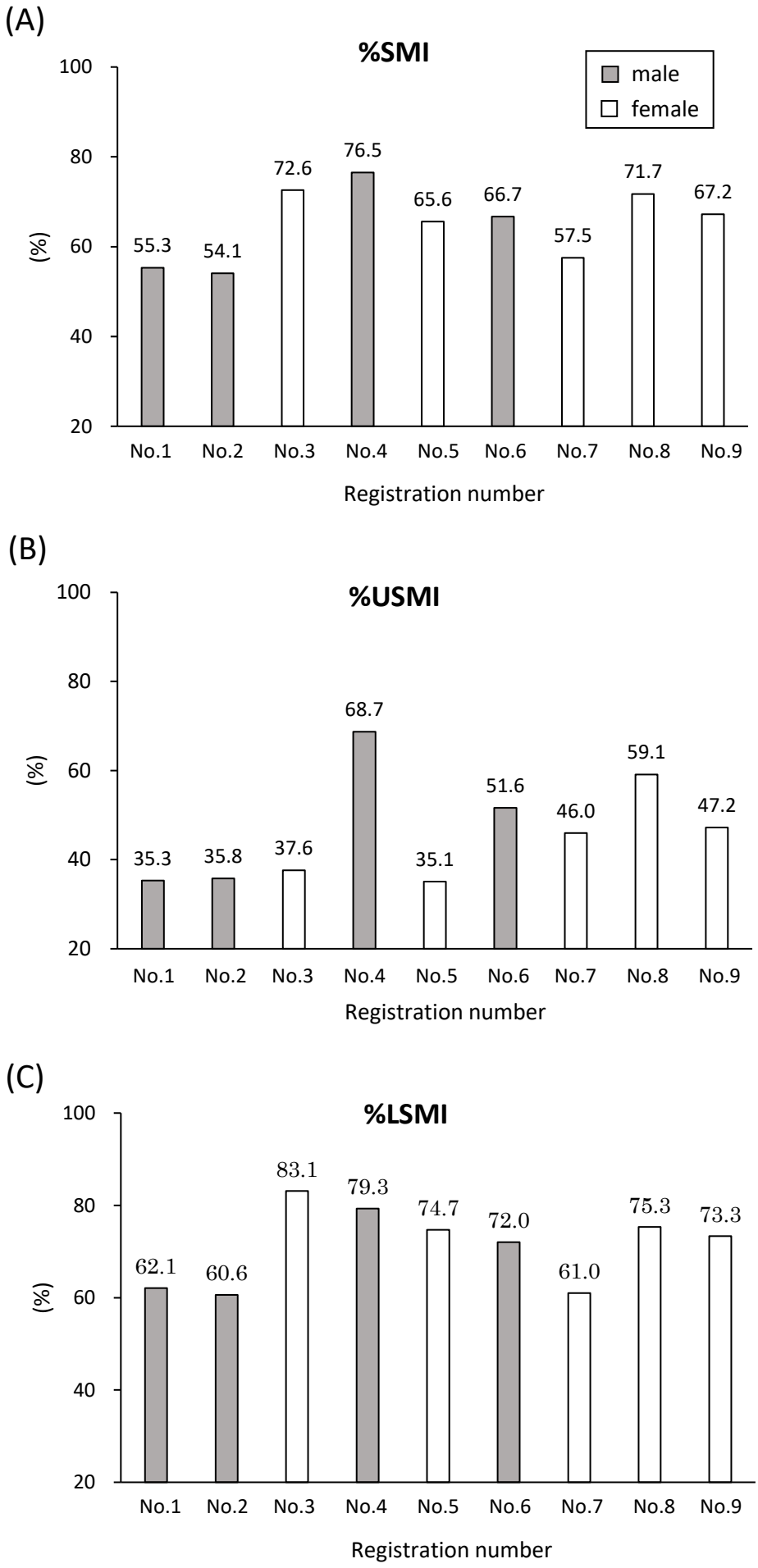

(A)
%SMI
male
female
100
80
60
40
20
(%)
55.3
54.1
72.6
76.5
65.6
66.7
57.5
71.7
67.2
No.1
No.2
No.3
No.4
No.5
No.6
No.7
No.8
No.9
Registration number
(B)
%USMI
100
80
60
40
20
(%)
35.3
35.8
37.6
68.7
35.1
51.6
46.0
59.1
47.2
No.1
No.2
No.3
No.4
No.5
No.6
No.7
No.8
No.9
Registration number
(C)
%LSMI
100
80
60
40
20
(%)
62.1
60.6
83.1
79.3
74.7
72.0
61.0
75.3
73.3
No.1
No.2
No.3
No.4
No.5
No.6
No.7
No.8
No.9
Registration number

Fig.2

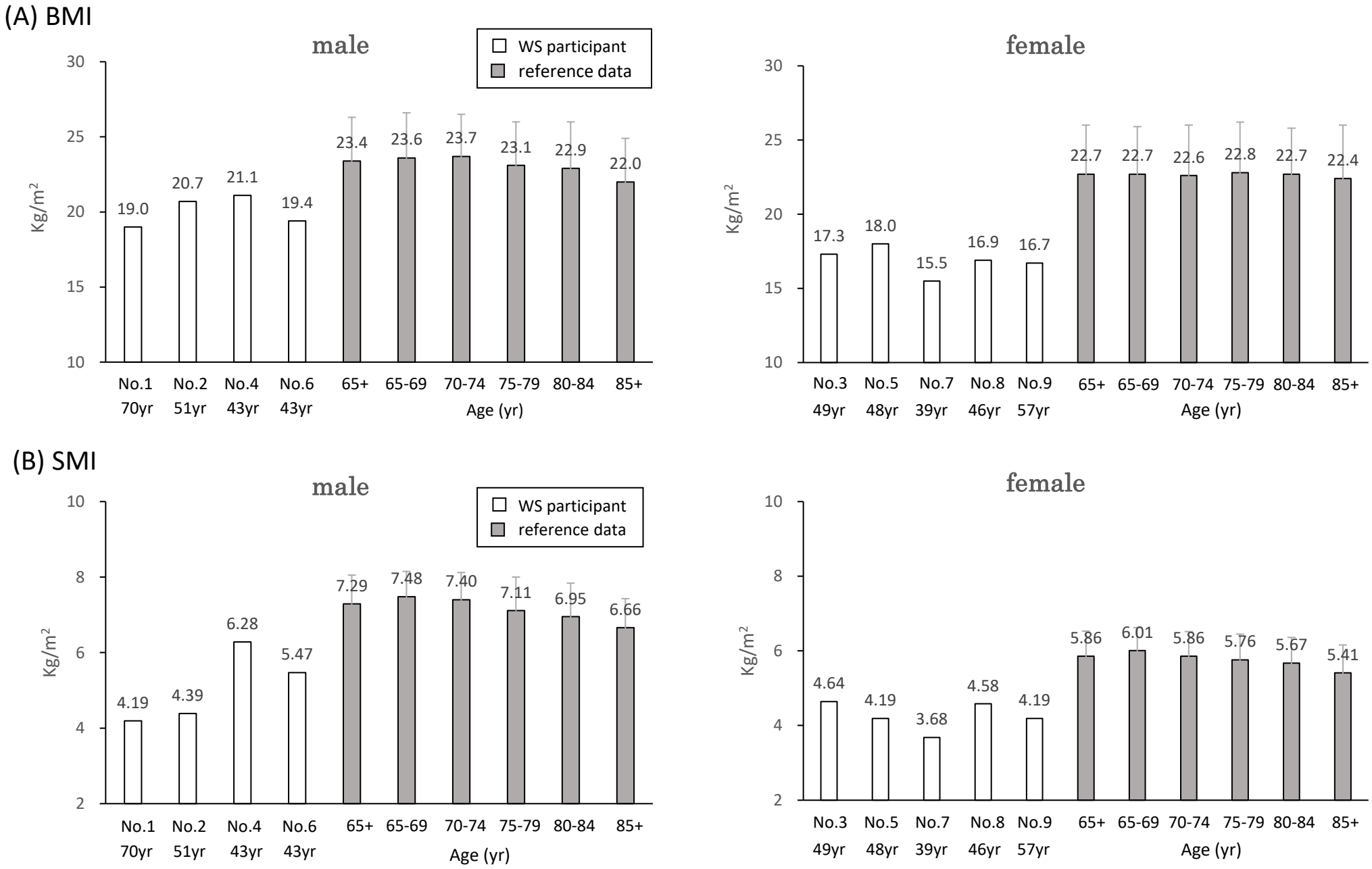
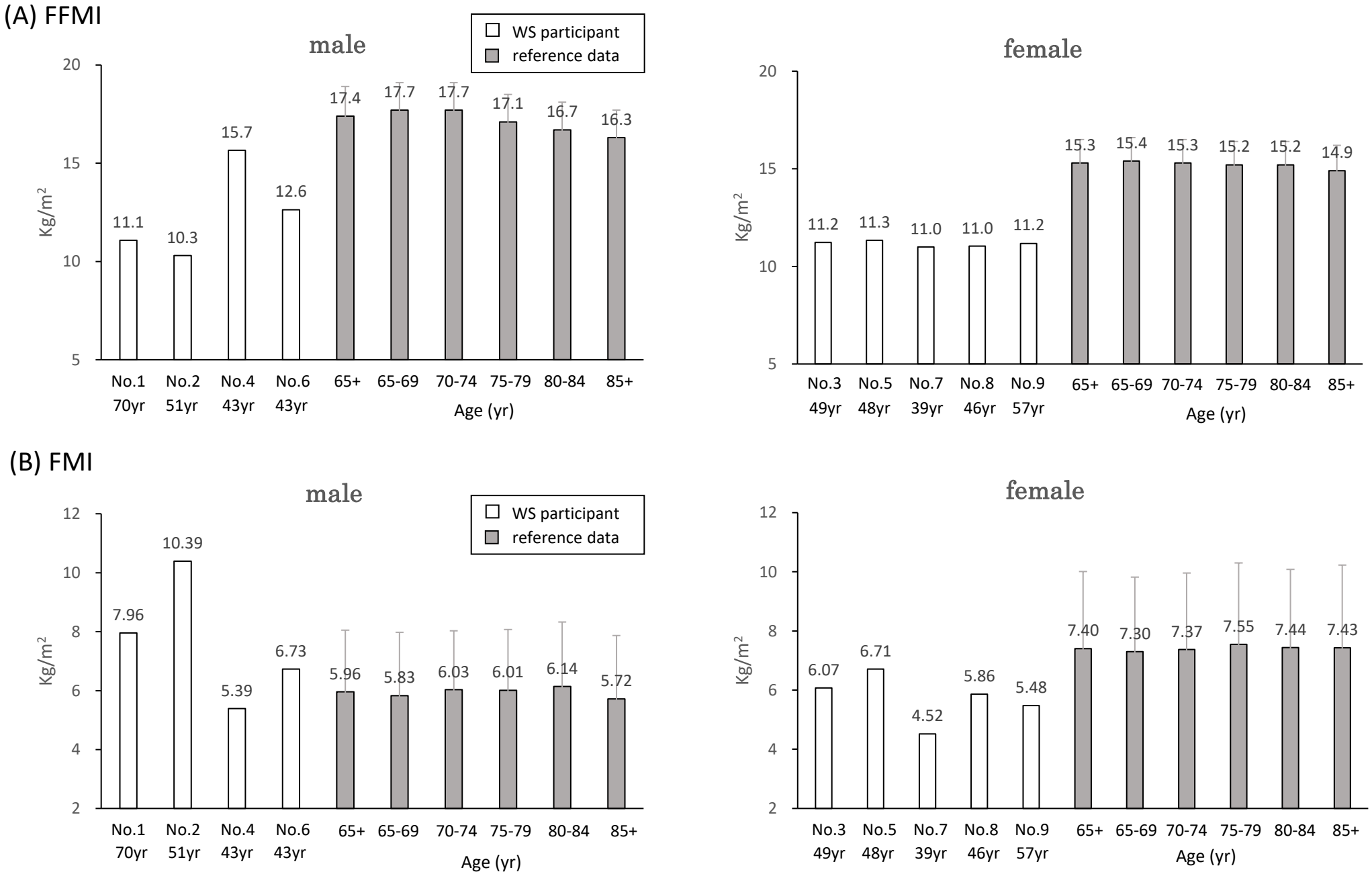

(A) BMI
male
WS participant
reference data
Kg/m2
30
25
20
15
10
19.0
20.7
21.1
19.4
23.4
23.6
23.7
23.1
22.9
22.0
No.1 70yr
No.2 51yr
No.4 43yr
No.6 43yr
65+
65-69
70-74
75-79
80-84
85+
Age (yr)
female
17.3
18.0
15.5
16.9
16.7
22.7
22.7
22.6
22.8
22.7
22.4
No.3 49yr
No.5 48yr
No.7 39yr
No.8 46yr
No.9 57yr
(B) SMI
male
4.19
4.39
6.28
5.47
7.29
7.48
7.40
7.11
6.95
6.66
female
4.64
4.19
3.68
4.58
4.19
5.86
6.01
5.86
5.76
5.67
5.41

Fig.3


(A) FFMI
male
WS participant
reference data
Kg/m2
20
15
10
5
11.1
10.3
15.7
12.6
17.4
17.7
17.7
17.1
16.7
16.3
No.1 70yr
No.2 51yr
No.4 43yr
No.6 43yr
65+
65-69
70-74
75-79
80-84
85+
Age (yr)
female
11.2
11.3
11.0
11.0
11.2
15.3
15.4
15.3
15.2
15.2
14.9
No.3 49yr
No.5 48yr
No.7 39yr
No.8 46yr
No.9 57yr
(B) FMI
male
12
10
8
6
4
2
7.96
10.39
5.39
6.73
5.96
5.83
6.03
6.01
6.14
5.72
female
6.07
6.71
4.52
5.86
5.48
7.40
7.30
7.37
7.55
7.44
7.43