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Dose–response relationships of sarcopenia parameters with incident disability and mortality in older Japanese adults

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Abstract

Background Sarcopenia-related parameters may have differential impacts on health-related outcomes in older adults. We examined dose–response relationships of body composition, muscle strength, and physical performance with incident disability and mortality.

Methods This prospective study included 1765 Japanese residents (862 men; 903 women) aged ≥65 years who participated in health check-ups. Outcomes were incident disability and all-cause mortality. Fat mass index (FMI) and skeletal muscle mass index (SMI), determined using segmental multi-frequency bioelectrical impedance analysis, handgrip strength (HGS), and usual gait speed (UGS) were measured. We determined multivariate-adjusted hazard ratios (HRs) for disability and mortality relative to sex-specific reference values (FMI: medians; SMI: 7.0 kg/m^2 for men and 5.7 kg/m^2 for women; HGS: 28 kg for men and 18 kg for women; or UGS: 1.0 m/s for both sexes). Association shapes were examined using restricted cubic splines or fractional polynomial functions.

Results The median follow-up was 5.3 years; 107 (12.7%) men and 123 (14.2%) women developed disability, and 101 (11.7%) men and 56 (6.2%) women died. FMI did not impact any outcome in men and disability in women, while an FMI ≤ 7.3 kg/m^2 (median) was significantly associated with higher mortality risk in women, compared with median FMI. SMI did not impact disability in either sex and mortality in women, but showed a significant inverse dose–response relationship with mortality risk in men [HRs (95% confidence intervals) of minimum and maximum values compared with the reference value: 2.18 (1.07–4.46) and 0.43 (0.20–0.93), respectively], independent of HGS and UGS. HGS and UGS showed a significant inverse dose–response relationship with disability in both sexes [HGS: 1.71 (1.00–2.91) and 0.31 (0.09–0.99), respectively, in men, 2.42 (1.18–4.96) and 0.41 (0.20–0.85), respectively, in women; UGS: 2.14 (1.23–3.74) and 0.23 (0.08–0.67), respectively, in men, 3.26 (2.07–5.14) and 0.11 (0.05–0.26), respectively, in women] and mortality in women [HGS: 6.84 (2.84–16.47) and 0.06 (0.02–0.21), respectively; UGS: 2.67 (1.14–6.27) and 0.30 (0.11–0.85), respectively], independent of body composition, but did not impact mortality in men.

Conclusions Disability risk was more dependent on muscle strength and physical performance in both sexes. Mortality risk in men was more dependent on muscle mass, and mortality risk in women was influenced by lower fat mass along with muscle strength and physical performance. Although improving muscle strength and physical performance should be the first target for health promotion, it is also necessary to pay attention to body composition to extend life expectancy in older adults.

Keywords Sarcopenia; Skeletal muscle; Handgrip strength; Gait speed; Disability; Mortality

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Introduction

Sarcopenia was originally defined as an age-related loss of skeletal muscle mass in older adults.[1,2] Since 2010, several working groups have proposed conceptual and operational definitions of sarcopenia, including muscle mass, muscle strength, and/or physical performance.[3–9] In 2020, the Sarcopenia Definition and Outcomes Consortium[10] stated that weakness, defined by low handgrip strength (HGS), as well as slowness, defined by low usual gait speed (UGS), should be included in the definition of sarcopenia. However, they were sceptical about including the muscle mass. Thus, the focus of the definition of sarcopenia has shifted from skeletal muscle mass to strength and physical performance over the last two decades.

These trends are attributable to the evidence showing that muscle strength and physical performance are more strongly associated with health-related outcomes than muscle mass.[11,12] Although previous studies have shown that muscle mass only partially accounts for the muscle strength–mortality association,[13] evidence on whether muscle mass–outcome associations are mediated by muscle strength and physical performance is limited.[14] Moreover, fat mass is a critical confounder of these associations.[14,15] However, many of the studies[11,12] have not sufficiently accounted for this impact. Additionally, there is an absolute shortage of Asian data in previous findings.[11,12] Population-specific investigations are warranted because the characteristics of body composition and prevalence of obesity vary by population.[16] Finally, although the associations of body composition, muscle strength, and physical performance with health-related outcomes have been examined using categorical or linear approaches in previous studies,[13,14,17,18] the true shape of the association is unknown. If the true shape is not linear, these approaches may mask or weaken significant associations. The cubic spline analysis, which has high precision,[19] reveals a more elaborate shape of the association than that possible with these approaches.

Therefore, we examined the shapes of the associations of body composition, muscle strength, and physical performance, after accounting for the confounding effects of each on the other, with incident disability and all-cause mortality among community-dwelling older Japanese adults. Specifically, we aimed to clarify (i) whether body composition, muscle strength, and physical performance have differential impacts on incident disability and mortality and (ii) whether their impacts differ between sexes because of the previously established sex-related differences in body composition, muscle strength, and physical performance.[20]

Methods

Study population

We used combined data[21,22] from the Kusatsu Longitudinal Study[23] and the Hatoyama Cohort Study.[24] We extracted the baseline data of 1944 participants (1250 from Kusatsu and 694 from Hatoyama) aged ≥ 65 years, for whom information on body composition, muscle strength, and physical performance was collected at an initial check-up between 2008 and 2016 in Kusatsu and 2010 and 2014 in Hatoyama. A total of 179 participants were excluded because of non-standard body composition findings or missing data. Ultimately, 1765 participants (862 men and 903 women) without disabilities were included.

Measurements

Body composition parameters

Body composition parameters were measured using direct segmental multi-frequency bioelectrical impedance analysis (InBody 720 analyser, InBody Co. Ltd., Seoul, Korea)[25] using a tetrapolar, 8-point tactile electrode system that separately measures impedance of the arms, trunk, and legs at six different frequencies (1, 5, 50, 250, 500, and 1000 kHz). The InBody 720 automatically estimates weight, body mass index (BMI), fat mass, and lean soft-tissue mass (LSTM) of the arms and legs. The appendicular LSTM was calculated as the sum of the LSTM of the arms and legs. To determine the fat mass index (FMI)[26] and skeletal muscle mass index (SMI),[2] the fat mass and appendicular LSTM were normalized by height in meters squared.

Muscle strength and physical performance

To measure muscle strength, HGS was assessed using a Smedley-type hand dynamometer (Yagami Co., Tokyo, Japan).[27] Participants stood with their arms hanging naturally at their sides, holding the dynamometer with a grip size adjusted to a comfortable level. They were instructed and verbally encouraged to squeeze the dynamometer as hard as possible.[27] Participants performed two trials with the dominant hand, and the best result (to the nearest 0.1 kg) was used.

For physical performance measurements, UGS was measured over a distance of 5 m, with acceleration and deceleration phases of 3 m each.[27] Participants were instructed to

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stand with their feet behind but just touch a stationary starting line marked with a tape strip at 0 m. On the tester's command, they were to start walking at their normal pace along an 11-m course. The actual walking time was measured over 5 m and was started when the participant's trunk had passed the 3-m mark and ended when the trunk was beyond the 8-m mark.[27] UGS was measured only once and calculated as the distance divided by the time taken to walk that distance (m/s).

All-cause mortality and disability

We ascertained the occurrence of disability and/or all deaths on 13 December 2017, in Kusatsu town and 31 December 2015, in Hatoyama town. All-cause mortality was confirmed by checking local registries that have linked records with the Japanese National Vital Statistics System.

Disability was identified in the participants using the nationally unified database of the long-term care insurance (LTCI) system, enrolment in which is mandatory for all Japanese adults aged $\geq$ 40 years. The system provides formal care and support for eligible Japanese adults aged $\geq$ 65 years with physical and mental disabilities.[28,29] LTCI certification is based on a nationally standardized multistep assessment.[28,29] Ultimately, the Municipal Certification Committee of Needed Long-Term Care decides whether an older adult should be certified as requiring long-term care and classifies care needs under one of seven levels (support level, 1–2; care level, 1–5). Disability was defined as the onset of long-term care needs at the support level 1 or above,[30] using the date of the LTCI application as the date of the disability incident.[22]

Covariates

The covariates included baseline age, study area (Kusatsu or Hatoyama), year of first visit for health check-up, alcohol consumption and tobacco smoking status (current, never, or former), previous diagnosis of stroke, heart disease, cancer, hypertension (systolic blood pressure $\geq$ 140 mmHg and/or diastolic blood pressure $\geq$ 90 mmHg; previous diagnosis or ongoing medical treatment), and diabetes (haemoglobin A1c $\geq$ 6.5%; previous diagnosis or ongoing medical treatment), high total cholesterol ($\geq$240 mg/dL or ongoing medical treatment), low total cholesterol ($<$160 mg/dL), hypoalbuminemia ($<$3.8 g/dL), anaemia (haemoglobin $<$ 13.0 g/dL in men or $<$12.0 g/dL in women), and chronic kidney disease (estimated glomerular filtration rate $<$ 60 mL/min/1.73 m^2, calculated using creatinine concentration and equations developed for Japanese adults[31]), low activity (an answer of 'less than once a day' to the question 'How often do you usually go outdoors?'[22]), depressed mood (short form of the Geriatric Depression Scale $\geq$ 5[32]), and cognitive impairment (Mini-Mental State Examination score $\leq$ 23[33]).

Statistical analyses

All data were analysed by sex using Stata 16.1 (StataCorp, TX, USA). Statistical significance was set at α = 0.05. Descriptive statistics were used to characterize the participants. The unpaired *t*-test, Mann–Whitney *U*-test, and χ^2 test were used to compare the baseline characteristics of independent participants and those with disability or death.

For primary analysis, we used the Cox proportional hazards model, with incident disability or mortality as the dependent variable and FMI, SMI, HGS, and UGS as independent variables. We then constructed two multivariate analytic models and examined multivariate-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) in terms of FMI, SMI, HGS, and UGS for incident disability or mortality. Model 1 was adjusted for baseline age, study area, year of first visit for health check-up, alcohol consumption and smoking status, hypertension, stroke, heart disease, diabetes, cancer, high total cholesterol, low total cholesterol, hypoalbuminemia, anaemia, chronic kidney disease, low activity, depressed mood, and cognitive impairment. In the analyses with FMI and SMI as independent variables, these two indices were mutually adjusted as were other covariates because they are mutual confounders and both have sex-specific differences.[15,34] Moreover, to examine the independent impacts of body composition, muscle strength, and physical performance on outcomes, Model 2 was adjusted for HGS and UGS in the analysis with FMI or SMI as an independent variable or with FMI and SMI in the analysis with HGS or UGS as an independent variable, in addition to the variables in Model 1.

Furthermore, using fractional polynomial (FP) functions or restricted cubic spline (RCS), in accordance with the procedures of previous studies,[21,35] we examined the dose–response relationship of FMI, SMI, HGS, and UGS independently with incident disability or mortality risk. For the FP procedure, the power transformation was performed by setting the default values of Stata, namely, -2, -1, -0.5, 0, 0.5, 1, 2, and 3. For the RCS, the knot locations were chosen as 3, 4, or 5. We used the Akaike information criterion to select the FP transformation or RCS with 3, 4, or 5 knots and adopted the model with the lowest Akaike information criterion value.[36] We set the median FMI or cut-off points for sarcopenia criteria defined by the Asian Working Group for Sarcopenia in 2019 (SMI: 7.0 kg/m^2 for men and 5.7 kg/m^2 for women; HGS: 28 kg for men and 18 kg for women; or UGS: 1.0 m/s for both sexes[9]), as the reference value for each model.

In the secondary analyses of the possible influence of reverse causation on the association between each measure and disability or mortality, we performed sensitivity analyses using the same statistical approach, after excluding disability or death that occurred during the first year and the first 2 years of follow-up.

Results

During a median (interquartile range) follow-up of 5.3 (3.5–6.9) years, 107 (12.7%) men and 123 (14.2%) women presented with functional disabilities, with disability rates of 24.3 and 25.5 per 1000 person-years, respectively. Of these, 9 (8.4%) men and 14 (11.4%) women presented with disabilities during the first year, and 22 (20.6%) men and 26 (21.1%) women presented with disabilities during the first 2 years. During a median follow-up of 5.3 (4.4–7.5) years, 101 (11.7%) men and 56 (6.2%) women died, with mortality rates of 21.5 and 10.4 per 1000 person-years, respectively. Of these, 2 (2.0%) men and 2 (3.6%) women died during the first year, and 6 (5.9%) men and 5 (8.9%) women died during the first 2 years.

Tables 1–2 show the baseline characteristics of the study population according to sex and disability status (*Table* 1) and according to sex and survival status (*Table* 2). Independent participants and those with disability or death consistently and significantly differed in baseline age, study area, total cholesterol and albumin levels, estimated glomerular filtration rate, Mini-Mental State Examination score, height, weight, appendicular LSTM, SMI, HGS, UGS, and prevalence of low total cholesterol in both sexes. In men, independent participants and those with disability significantly differed in alcohol consumption status, haemoglobin A1c, and prevalence of diabetes and high total cholesterol (*Table* 1), while survivors and non-survivors showed significant differences in haemoglobin and BMI (*Table* 2). Consistent and significant differences were observed in diastolic blood pressure and the prevalence of hypoalbuminemia, anaemia and chronic kidney disease in men (*Tables* 1–2). In women, independent participants and those with disability significantly differed in haemoglobin level and the prevalence of hypertension, stroke, and anaemia (*Table* 1), while survivors and non-survivors significantly differed in diastolic blood pressure and the prevalence of hypoalbuminemia and chronic kidney disease (*Table* 2). Consistent and significant differences were observed in the Geriatric Depression Scale scores and the prevalence of high total cholesterol, low activity, depressive symptoms, and cognitive impairment (*Tables* 1–2).

Figure 1 shows the dose–response relationships of FMI with incident disability and mortality risks. FMI consistently had no impact on disability and mortality in the first multivariate model (Model 1) and the additional adjustment model for HGS and UGS (Model 2) in men (*Figure* 1A–1D). In women, although FMI had no impact on disability in both models (*Figure* 1E–1F) and mortality in Model 1 (*Figure* 1G), FMI $\leq$ 7.3 kg/m^2 (median) was significantly associated with higher mortality risk in Model 2 [HR (95% CI) of minimum value (2.1 kg/m^2) compared with reference value (7.3 kg/m^2): 3.56 (1.11–11.40) (*Figure* 1H)].

Figure 2 shows the dose–response relationships of SMI with incident disability and mortality risks. SMI did not impact disability in either sex and mortality in women in both models (*Figure* 2A, 2B, and 2E–2H). However, SMI had significant inverse dose–response relationships with mortality risk consistently in both Models in men [HRs (95% CIs) of minimum (4.8 kg/m^2) and maximum (9.4 kg/m^2) values compared with reference value (7.0 kg/m^2): 2.45 (1.20–5.02) and 0.38 (0.17–0.82), respectively in model 1 (*Figure* 2C); 2.18 (1.07–4.48) and 0.43 (0.20–0.93), respectively in model 2 (*Figure* 2D)].

Figure 3 shows the dose–response relationships of HGS with incident disability and mortality risks. HGS had significant inverse dose–response relationships with disability and mortality risk consistently in Model 1 in both sexes (*Figure* 3A, 3C, 3E, and 3G). Although the significant inverse HGS–disability association persisted even after further adjustment for FMI and SMI in men [HRs (95% CIs) of minimum (14 kg) and maximum (59 kg) values compared with reference value (28 kg): 1.71 (1.00–2.91) and 0.31 (0.09–0.99), respectively (*Figure* 3B)], the significant HGS–mortality association disappeared (*Figure* 3D). HGS in women consistently showed significant inverse dose–response relationships with disability [HRs (95% CIs) of minimum (6 kg) and maximum (36.5 kg) values compared with the reference value (18 kg): 2.42 (1.18–4.96) and 0.41 (0.20–0.85), respectively] and mortality [HRs (95% CIs) of minimum (5.5 kg) and maximum (36.5 kg) values compared with the reference value (18 kg): 6.84 (2.84–16.47) and 0.06 (0.02–0.21), respectively] risk even after adjusting for FMI and SMI (*Figure* 3F and 3H).

Figure 4 shows the dose–response relationships of UGS with incident disability and mortality risks. UGS consistently showed a significant inverse dose–response relationship with disability in both sexes [HRs (95% CIs) of minimum and maximum values compared with the reference value (1.0 m/s): 2.14 (1.23–3.74) and 0.23 (0.08–0.67), respectively, in men (*Figure* 4B); 3.26 (2.07–5.14) and 0.11 (0.05–0.26), respectively, in women (*Figure* 4F)]. Although UGS in women also showed a significant inverse dose–response relationship with mortality even after further adjustment for FMI and SMI [HRs (95% CIs) of minimum and maximum values compared with the reference value (1.0 m/s): 2.67 (1.14–6.27) and 0.30

Table 1 Baseline characteristics of the study population according to sex and disability status

Variables	Mean ± SD or *n* (%)					
	Men (*n* = 844)			Women (*n* = 867)		
	No incident disability (*n* = 737)	Incident disability (*n* = 107)	*P* value	No incident disability (*n* = 744)	Incident disability (*n* = 123)	*P* value
Age (years)	70.8 ± 4.8	78.0 ± 6.2	<**0.001**	70.5 ± 5.2	76.9 ± 6.1	<**0.001**
65–74	574 (77.9)	28 (26.2)	<**0.001**	579 (77.8)	41 (33.3)	<**0.001**
75^{+}	163 (22.1)	79 (73.8)		165 (22.2)	82 (66.7)	
Study area			**0.001**			**0.001**
Kusatsu	414 (56.2)	83 (77.6)		510 (68.6)	102 (82.9)	
Hatoyama	323 (43.8)	24 (22.4)		234 (31.4)	21 (17.1)	
Alcohol consumption status			**0.020**			0.09
Current	514 (69.7)	61 (57.0)		295 (39.7)	36 (29.3)	
Former	71 (9.6)	10 (9.4)		53 (7.1)	8 (6.5)	
Never	117 (15.9)	26 (24.3)		356 (47.9)	68 (55.3)	
Missing	35 (4.8)	10 (9.4)		40 (5.4)	11 (8.9)	
Smoking status			0.16			0.39
Current	146 (19.8)	22 (20.6)		64 (8.6)	12 (9.8)	
Former	361 (49.0)	44 (41.1)		66 (8.9)	8 (6.5)	
Never	195 (26.4)	31 (29.0)		573 (77.0)	92 (74.8)	
Missing	35 (4.8)	10 (9.3)		41 (5.5)	11 (8.9)	
SBP (mmHg)	138 ± 22	138 ± 20	0.69	136 ± 22	138 ± 23	0.18
DBP (mmHg)	80 ± 12	78 ± 12	**0.026**	77 ± 12	76 ± 12	0.26
Hypertension[a]	490 (66.5)	72 (67.3)	0.87	442 (59.4)	92 (74.8)	**0.001**
Stroke	41 (5.6)	11 (10.3)	0.06	25 (3.4)	9 (7.3)	**0.036**
Heart disease	120 (16.3)	19 (17.8)	0.70	80 (10.8)	10 (8.1)	0.38
Cancer	75 (10.2)	12 (11.2)	0.74	59 (7.9)	8 (6.5)	0.58
Haemoglobin A1c (%)	5.5 ± 0.7	5.8 ± 1.1	<**0.001**	5.5 ± 0.6	5.4 ± 0.6	0.27
Diabetes[b]	143 (19.4)	34 (31.8)	**0.003**	80 (10.8)	18 (14.6)	0.21
Total cholesterol (mg/dL)	198 ± 33	190 ± 38	**0.021**	215 ± 34	203 ± 38	<**0.001**
High total cholesterol[c]	180 (24.4)	17 (15.9)	**0.049**	346 (46.5)	44 (35.8)	**0.027**
Low total cholesterol[d]	87 (11.8)	21 (19.6)	**0.024**	29 (3.9)	10 (8.1)	**0.036**
Albumin (g/dL)	4.3 ± 0.2	4.1 ± 0.3	<**0.001**	4.3 ± 0.3	4.2 ± 0.3	<**0.001**
Hypoalbuminemia[e]	34 (4.6)	22 (20.6)	<**0.001**	32 (4.3)	8 (6.5)	0.28
Haemoglobin (g/dL)	14.4 ± 1.3	14.1 ± 1.6	0.06	13.2 ± 1.1	12.9 ± 1.3	**0.007**
Anaemia[f]	99 (13.4)	22 (20.6)	**0.049**	80 (10.8)	21 (17.1)	**0.043**
eGFR (mL/min/1.73 m^2)	68.8 ± 13.9	62.8 ± 14.0	<**0.001**	68.2 ± 13.4	65.0 ± 17.9	**0.024**
Chronic kidney disease[g]	185 (25.1)	43 (40.2)	**0.001**	193 (25.9)	41 (33.3)	0.09
Low activity[h]	20 (2.7)	4 (3.7)	0.55	27 (3.6)	11 (8.9)	**0.008**
GDS score	2.7 ± 2.6	3.1 ± 2.5	0.11	2.9 ± 2.7	4.3 ± 3.1	<**0.001**
Depressive symptoms[i]	151 (20.5)	27 (25.2)	0.26	171 (23.0)	45 (36.6)	**0.001**
MMSE score	27.9 ± 2.3	26.7 ± 2.7	<**0.001**	28.3 ± 2.1	26.6 ± 3.9	<**0.001**
Cognitive impairment[j]	31 (4.2)	9 (8.4)	0.06	20 (2.7)	15 (12.2)	<**0.001**
Height (cm)	163.0 ± 5.8	160.2 ± 6.6	<**0.001**	150.3 ± 5.5	146.8 ± 6.1	<**0.001**
Weight (kg)	62.5 ± 9.0	59.6 ± 8.9	**0.002**	51.9 ± 7.9	49.7 ± 8.2	**0.004**
BMI (kg/m^2)	23.5 ± 2.9	23.2 ± 2.8	0.27	23.0 ± 3.2	23.0 ± 3.4	0.93
Fat mass (kg)	15.4 ± 5.5	15.8 ± 5.6	0.43	16.8 ± 5.8	16.4 ± 5.9	0.40
FMI (kg/m^2)	5.8 ± 2.1	6.2 ± 2.2	0.07	7.5 ± 2.5	7.6 ± 2.8	0.57
Appendicular lean soft-tissue mass (kg)	19.7 ± 2.7	18.0 ± 2.9	<**0.001**	13.5 ± 2.0	12.4 ± 2.3	<**0.001**
SMI (kg/m^2)	7.4 ± 0.7	7.0 ± 0.7	<**0.001**	6.0 ± 0.6	5.8 ± 0.8	**0.003**
HGS (kg)	35.2 ± 6.3	30.0 ± 6.3	<**0.001**	21.8 ± 4.3	18.1 ± 5.1	<**0.001**
UGS (m/s)	1.36 ± 0.23	1.24 ± 0.23	<**0.001**	1.36 ± 0.23	1.16 ± 0.25	<**0.001**

BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FMI, fat mass index; GDS, Geriatric Depression Scale; HGS, handgrip strength; MMSE, Mini-Mental State Examination; SBP, systolic blood pressure; SD, standard deviation; SMI, skeletal muscle mass index; UGS, usual gait speed.

[a]Hypertension: SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg or previous diagnosis or current medical treatment.

[b]Diabetes: haemoglobin A1c ≥ 6.5% or current medical treatment.

[c]High total cholesterol: ≥240 mg/dL or current medical treatment.

[d]Low total cholesterol: <160 mg/dL.

[e]Hypoalbuminemia: albumin <3.8 g/dL.

[f]Anaemia: haemoglobin < 13.0 g/dL in men and <12.0 g/dL in women.

[g]Chronic kidney disease: eGFR < 60 mL/min/1.73 m^2.

[h]Low activity: going outdoors < 1 time/week.

[i]Depressive mood (GDS score ≥ 5).

[j]Cognitive impairment (MMSE score ≤ 23).

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Table 2 Baseline characteristics of the study population according to sex and survival status

Variables	Mean ± SD or *n* (%)					
	Men (*n* = 862)			Women (*n* = 903)		
	Survivors (*n* = 761)	Non-survivors (*n* = 101)	*P* value	Survivors (*n* = 847)	Non-survivors (*n* = 56)	*P* value
Age (years)	71.2 ± 5.4	76.6 ± 6.5	<**0.001**	71.4 ± 5.7	77.6 ± 8.3	<**0.001**
65–74	572 (75.2)	36 (35.6)	<**0.001**	607 (71.7)	20 (35.7)	<**0.001**
75^{+}	189 (24.8)	65 (64.4)		240 (28.3)	36 (64.3)	
Study area			<**0.001**			**0.014**
Kusatsu	426 (56.0)	87 (86.1)		596 (70.4)	48 (85.7)	
Hatoyama	335 (44.0)	14 (13.9)		251 (29.6)	8 (14.3)	
Alcohol consumption status			0.17			0.13
Current	522 (68.6)	61 (60.4)		325 (38.4)	16 (28.6)	
Former	71 (9.3)	15 (14.9)		62 (7.3)	2 (3.6)	
Never	130 (17.1)	17 (16.8)		409 (48.3)	36 (64.3)	
Missing	38 (5.0)	8 (7.9)		51 (6.0)	2 (3.6)	
Smoking status			0.49			0.39
Current	149 (19.6)	23 (22.8)		73 (8.6)	5 (8.9)	
Former	372 (48.9)	44 (43.6)		69 (8.2)	8 (14.3)	
Never	202 (26.5)	26 (25.7)		653 (77.1)	41 (73.2)	
Missing	38 (5.0)	8 (7.9)		52 (6.1)	2 (3.6)	
SBP (mmHg)	138 ± 22	135 ± 21	0.26	136 ± 22	137 ± 23	0.54
DBP (mmHg)	80 ± 12	76 ± 13	<**0.001**	77 ± 12	73 ± 14	**0.020**
Hypertension[a]	509 (66.9)	66 (65.4)	0.76	523 (61.8)	35 (62.5)	0.91
Stroke	46 (6.0)	8 (7.9)	0.47	37 (4.4)	3 (5.4)	0.73
Heart disease	121 (15.9)	21 (20.8)	0.21	84 (9.9)	10 (17.9)	0.06
Cancer	78 (10.3)	12 (11.9)	0.61	65 (7.7)	6 (10.7)	0.41
Haemoglobin A1c (%)	5.5 ± 0.8	5.6 ± 0.8	0.38	5.5 ± 0.5	5.4 ± 1.2	0.89
Diabetes[b]	152 (20.0)	27 (26.7)	0.12	96 (11.3)	6 (10.7)	0.89
Total cholesterol (mg/dL)	198 ± 34	184 ± 35	<**0.001**	214 ± 35	198 ± 41	<**0.001**
High total cholesterol[c]	180 (23.7)	20 (19.8)	0.39	388 (45.8)	17 (30.3)	**0.024**
Low total cholesterol[d]	84 (11.0)	29 (28.7)	<**0.001**	36 (4.3)	6 (10.7)	**0.026**
Albumin (g/dL)	4.3 ± 0.3	4.1 ± 0.3	<**0.001**	4.3 ± 0.2	4.1 ± 0.4	<**0.001**
Hypoalbuminemia[e]	41 (5.4)	18 (17.8)	<**0.001**	33 (3.9)	12 (21.4)	<**0.001**
Haemoglobin (g/dL)	14.4 ± 1.3	14.0 ± 1.5	**0.021**	13.2 ± 1.1	12.9 ± 1.2	0.14
Anaemia[f]	103 (13.5)	22 (21.8)	**0.027**	100 (11.8)	10 (17.9)	0.18
eGFR (mL/min/1.73 m^2)	68.5 ± 14.0	63.6 ± 14.7	**0.001**	67.8 ± 14.0	62.4 ± 16.3	**0.007**
Chronic kidney disease[g]	195 (25.6)	41 (40.6)	**0.002**	226 (26.7)	28 (50.0)	<**0.001**
Low activity [h]	21 (2.8)	4 (4.0)	0.50	35 (4.1)	7 (12.5)	**0.004**
GDS score	2.7 ± 2.7	3.2 ± 2.7	0.08	3.1 ± 2.8	4.1 ± 3.1	**0.009**
Depressive symptoms[i]	158 (20.8)	29 (28.7)	0.07	214 (25.3)	21 (37.5)	**0.043**
MMSE score	27.8 ± 2.4	26.8 ± 2.9	<**0.001**	28.1 ± 2.6	26.6 ± 4.2	<**0.001**
Cognitive impairment[j]	36 (4.7)	9 (8.9)	0.08	36 (4.3)	7 (12.5)	**0.005**
Height (cm)	162.9 ± 5.9	159.7 ± 6.3	<**0.001**	149.7 ± 5.8	146.9 ± 6.6	<**0.001**
Weight (kg)	62.6 ± 9.0	57.6 ± 8.6	<**0.001**	51.6 ± 7.9	48.6 ± 8.5	**0.006**
BMI (kg/m^2)	23.6 ± 2.9	22.6 ± 3.0	**0.001**	23.0 ± 3.2	22.5 ± 3.5	0.23
Fat mass (kg)	15.5 ± 5.5	14.9 ± 5.6	0.26	16.8 ± 5.8	15.7 ± 5.9	0.18
FMI (kg/m^2)	5.9 ± 2.1	5.9 ± 2.2	0.95	7.5 ± 2.6	7.3 ± 2.7	0.53
Appendicular lean soft-tissue mass (kg)	19.7 ± 2.7	17.5 ± 2.6	<**0.001**	13.3 ± 2.1	12.3 ± 2.5	<**0.001**
SMI (kg/m^2)	7.4 ± 0.7	6.9 ± 0.7	<**0.001**	5.9 ± 0.7	5.7 ± 0.9	**0.004**
HGS (kg)	35.0 ± 6.5	29.8 ± 6.6	<**0.001**	21.3 ± 4.5	16.0 ± 5.4	<**0.001**
UGS (m/s)	1.35 ± 0.23	1.26 ± 0.23	<**0.001**	1.33 ± 0.25	1.10 ± 0.30	<**0.001**

BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FMI, fat mass index; GDS, Geriatric Depression Scale; HGS, handgrip strength; MMSE, Mini-Mental State Examination; SBP, systolic blood pressure; SD, standard deviation; SMI, skeletal muscle mass index; UGS, usual gait speed.

[a]Hypertension: SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg or previous diagnosis or current medical treatment.

[b]Diabetes: haemoglobin A1c ≥ 6.5% or current medical treatment.

[c]High total cholesterol: ≥240 mg/dL or current medical treatment.

[d]Low total cholesterol: <160 mg/dL.

[e]Hypoalbuminemia: albumin < 3.8 g/dL.

[f]Anaemia: haemoglobin < 13.0 g/dL in men and <12.0 g/dL in women.

[g]Chronic kidney disease: eGFR < 60 mL/min/1.73 m^2.

[h]Low activity: going outdoors < 1 time/week.

[i]Depressive mood (GDS score ≥ 5).

[j]Cognitive impairment (MMSE score ≤ 23).

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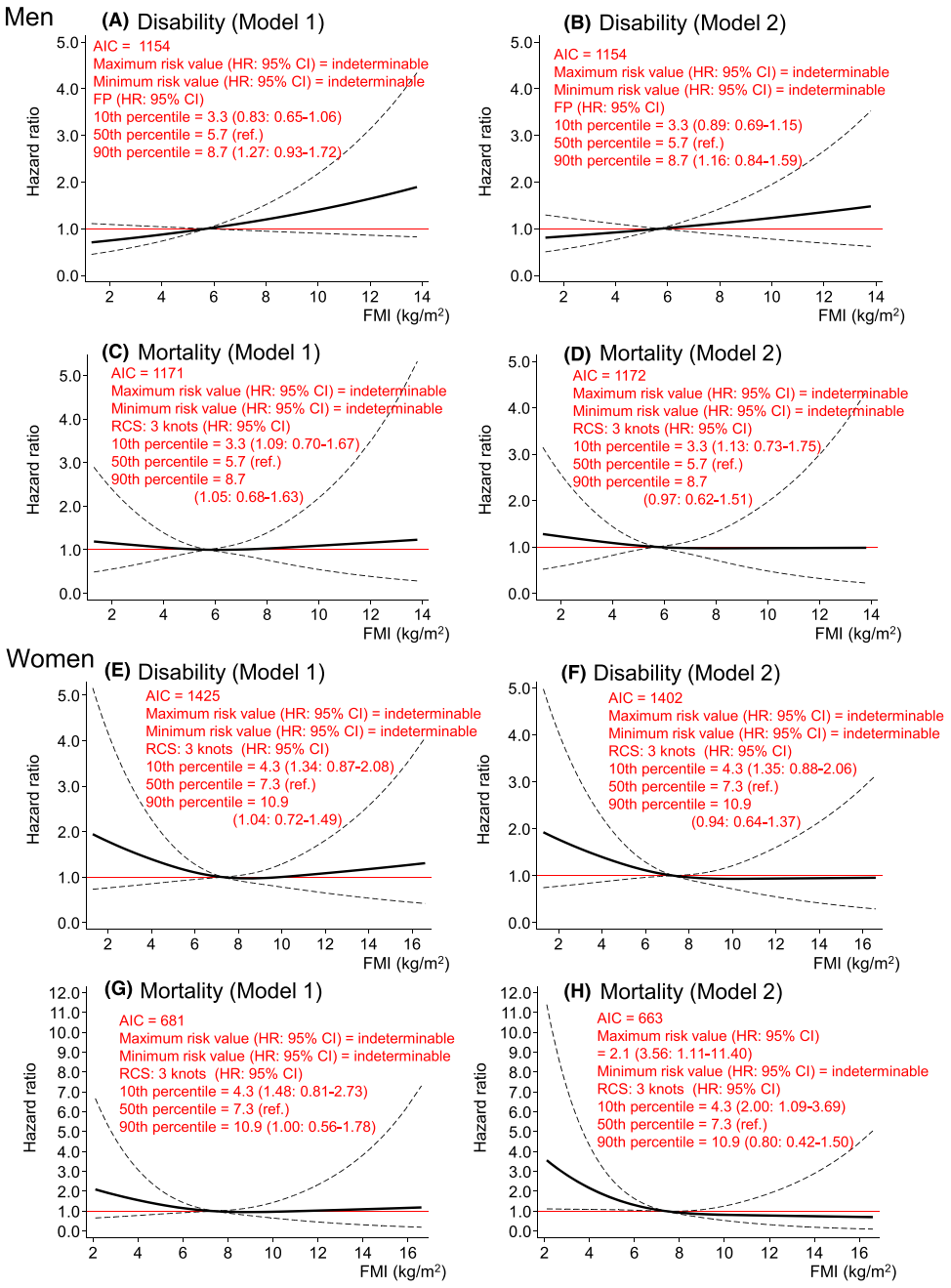

Figure 1 Dose–response relationships of FMI with incident disability and mortality risk. *Figure* 1A–1D shows the relationships of FMI with disability (*Figure* 1A–1B) and mortality (*Figure* 1C–1D) risks in men. *Figure* 1E–1H shows the relationships of FMI with disability (*Figure* 1E–1F) and mortality (*Figure* 1G–1H) risks in women. *Figure* 1A–1B was modelled using an FP function, and *Figure* 1C–1H was modelled using an RCS with three knots located at the 10th, 50th, and 90th percentiles of the distribution of the index. Model 1 was adjusted for baseline age, study area, year of first visit for health check-up, alcohol consumption and smoking status, hypertension, stroke, heart disease, diabetes, cancer, high total cholesterol, low total cholesterol, hypoalbuminemia, anaemia, chronic kidney disease, low activity, depressed mood, cognitive impairment, and SMI. Model 2 was adjusted for the variables in Model 1, plus HGS and UGS. The reference value for each model is the median FMI (i.e. FMI of 5.7 kg/m^2 in men and FMI of 7.3 kg/m^2 in women). The dashed lines indicate the 95% confidence intervals. AIC, Akaike's information criterion; FMI, fat mass index; FP, fractional polynomial; HGS, handgrip strength; HR, hazard ratio; SMI, skeletal muscle mass index; UGS, usual gait speed.

(0.11–0.85), respectively, in women (*Figure* 4H)], the significant UGS–mortality association disappeared in men (*Figure* 4D).

Results of the sensitivity analyses that excluded disability or death that occurred during the first year of follow-up were not substantially different from those of the primary analyses

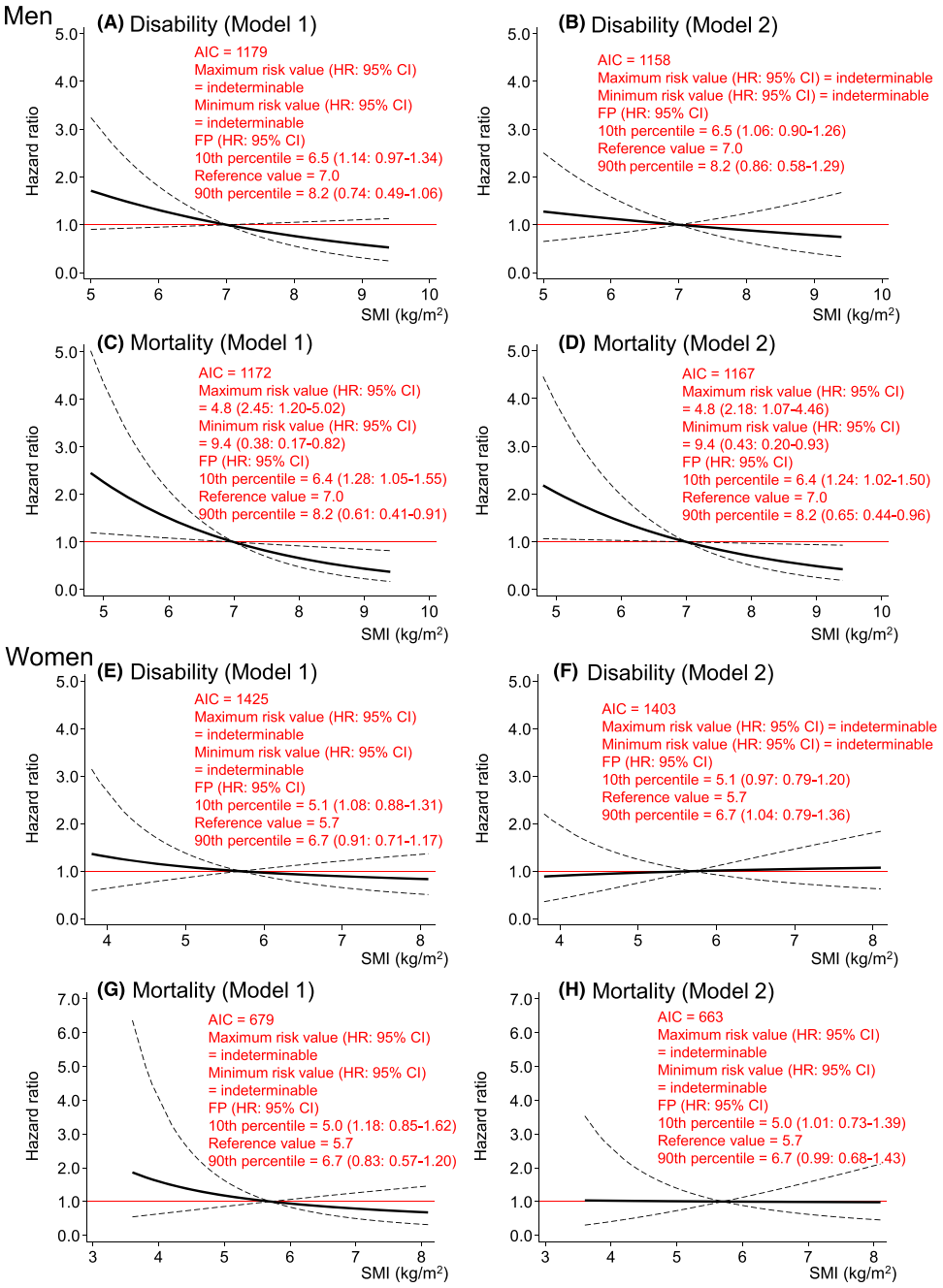

Figure 2 Dose–response relationships of SMI with incident disability and mortality risk. *Figure* 2A–2D shows the relationships of SMI with disability (*Figure* 2A–2B) and mortality (*Figure* 2C–2D) risks in men. *Figure* 2E–2H shows the relationships of SMI with disability (*Figure* 2E–2F) and mortality (*Figure* 2G–2H) risks in women. *Figure* 2A–2H was modelled using an FP function. Model 1 was adjusted for baseline age, study area, year of first visit for health check-up, alcohol consumption and smoking status, hypertension, stroke, heart disease, diabetes, cancer, high total cholesterol, low total cholesterol, hypoalbuminemia, anaemia, chronic kidney disease, low activity, depressed mood, cognitive impairment, and FMI. Model 2 was adjusted for the variables in Model 1, plus HGS and UGS. The reference values for each model are the cut-off points for sarcopenia criteria defined by the Asian Working Group for Sarcopenia in 2019 (i.e. SMI of 7.0 kg/m^2 in men and SMI of 5.7 kg/m^2 in women). The dashed lines indicate the 95% confidence intervals. AIC, Akaike's information criterion; FMI, fat mass index; FP, fractional polynomial; HGS, handgrip strength; HR, hazard ratio; SMI, skeletal muscle mass index; UGS, usual gait speed.

for both sexes (Supporting Information, *Figures* S1, S2, S3, & S4). In the analyses that excluded disability or death that occurred during the first 2 years, although the associations of SMI, HGS, and UGS with both outcomes were weakened in men, other results were not substantially different from those of the primary analyses (*Figures* S5, S6, S7, & S8).

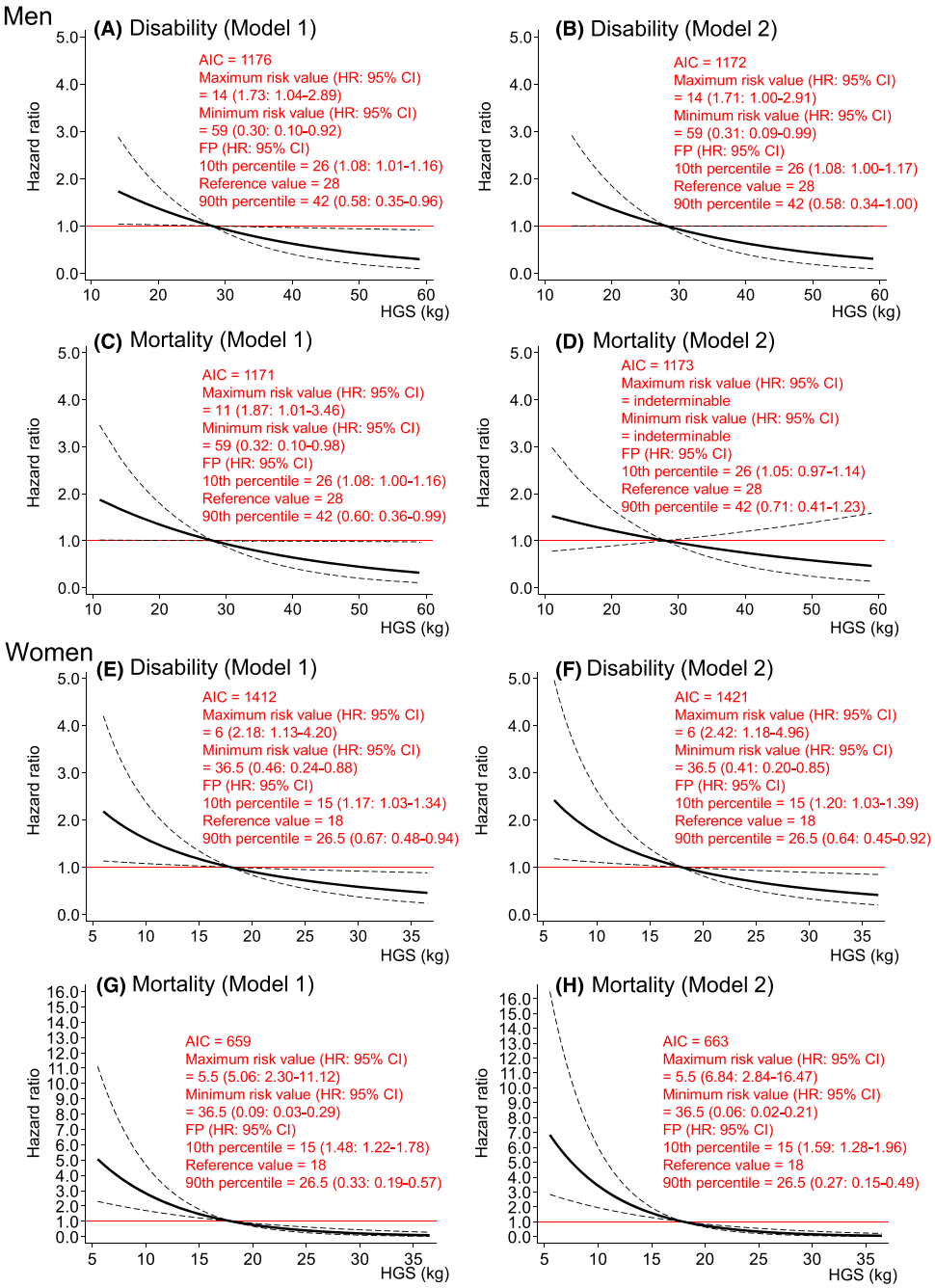

Figure 3 Dose–response relationships of HGS with incident disability and mortality risk. *Figure* 3A–3D shows the relationships of HGS with disability (*Figure* 3A–3B) and mortality (*Figure* 3C–3D) risks in men. *Figure* 3E–3H shows the relationships of HGS with disability (*Figure* 3E–3F) and mortality (*Figure* 3G–3H) risks in women. *Figure* 3A–3H was modelled using an FP function. Model 1 was adjusted for baseline age, study area, year of first visit for health check-up, drinking and smoking status, hypertension, stroke, heart disease, diabetes, cancer, high total cholesterol, low total cholesterol, hypoalbuminemia, anaemia, chronic kidney disease, low activity, depressed mood, and cognitive impairment. Model 2 was adjusted for the variables in Model 1, plus FMI and SMI. The reference values for each model are the cut-off points for sarcopenia criteria defined by the Asian Working Group for Sarcopenia in 2019 (i.e. HGS of 28 kg in men and HGS of 18 kg in women). The dashed lines indicate the 95% confidence intervals. AIC, Akaike's information criterion; FMI, fat mass index; FP, fractional polynomial; HGS, handgrip strength; HR, hazard ratio; SMI, skeletal muscle mass index.

Discussion

This sex-stratified multivariate dose–response analysis showed that FMI and SMI did not significantly impact disability risk, while HGS and UGS consistently exhibited an inverse dose–response relationship with disability in both sexes, independent of body composition. Conversely, sex-related differences were observed in the association of

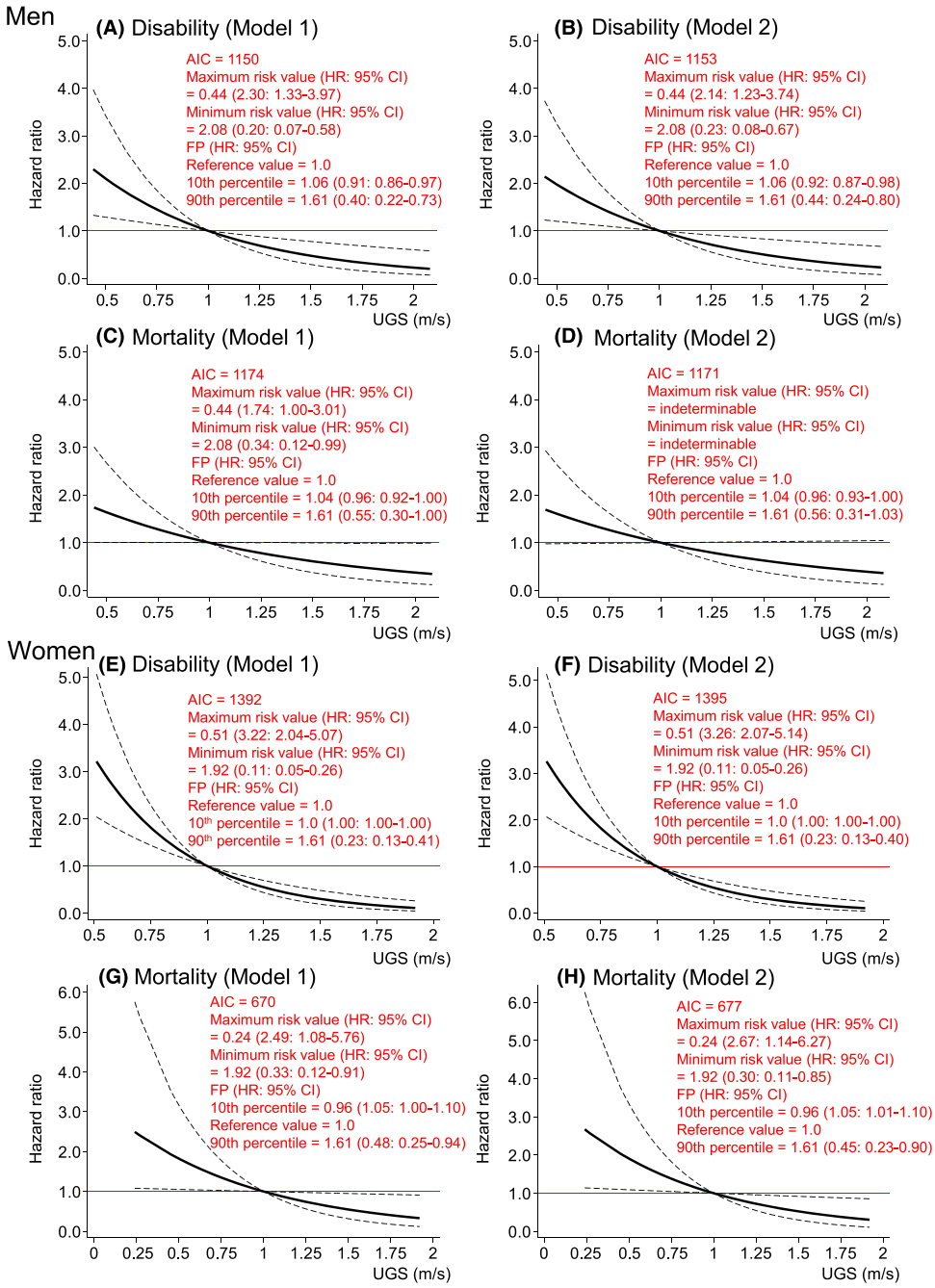

Figure 4 Dose–response relationships of UGS with incident disability and mortality risk. *Figure* 4A–4D shows the relationships of UGS with disability (*Figure* 4A–4B) and mortality (*Figure* 4C–4D) risks in men. *Figure* 4E–4H shows the relationships of UGS with disability (*Figure* 4E–4F) and mortality (*Figure* 4G–4H) risks in women. Figure 4A–4H was modelled using an FP function. Model 1 was adjusted for baseline age, study area, year of first visit for health check-up, drinking and smoking status, hypertension, stroke, heart disease, diabetes, cancer, high total cholesterol, low total cholesterol, hypoalbuminemia, anaemia, chronic kidney disease, low activity, depressed mood, and cognitive impairment. Model 2 was adjusted for the variables in Model 1, plus FMI and SMI. The reference values for each model are the cut-off points for sarcopenia criteria defined by the Asian Working Group for Sarcopenia in 2019 (i.e. UGS of 1.0 m/s in both sexes). The dashed lines indicate the 95% confidence intervals. AIC, Akaike's information criterion; FMI, fat mass index; FP, fractional polynomial; HR, hazard ratio; SMI, skeletal muscle mass index; UGS, usual gait speed.

each parameter with mortality risk. In men, the SMI–-mortality association remained significant even after HGS and UGS adjustments, whereas HGS– and UGS–mortality associations disappeared after body composition adjustment. FMI had no impact on mortality risk. In women, HGS and UGS consistently exhibited a clear inverse dose–response

relationship with disability and mortality, independent of body composition. Although SMI had no impact on mortality risk, a lower FMI was significantly associated with a higher mortality risk, independent of HGS and UGS.

We previously reported that fat-free mass index and SMI were more definitive predictors of mortality than BMI and FMI.[21] The results of men in the current study were consistent with those of this previous study.[21] However, in the current study, different results were observed in which the SMI–mortality association disappeared, and a lower FMI affected mortality risk in women. These discrepancies are attributable to adjustment for important covariates that have a strong impact on disability and mortality (i.e. low activity, depressive symptoms, cognitive impairment, HGS, and UGS) in addition to the covariates of our previous study.[21] Therefore, the results of the current study are considered more reasonable than that of our previous study.

Our results in women were consistent with those of previous studies that showed that muscle strength and physical performance are more strongly associated with health-related outcomes than muscle mass.[11,12,18] We provided further evidence that a lower FMI increases mortality risk, independent of HGS and UGS. Moreover, a noteworthy finding of this study was that in men, the disability risk was more dependent on muscle quality (i.e. HGS), while mortality risk was more dependent on muscle quantity (i.e. SMI). The annual rate of muscle strength decline has been reported to be approximately three times greater than the rates of concomitant loss of muscle mass, which is more pronounced in men than in women.[16] Therefore, early decline in muscle strength may have a stronger impact on disability, which is an outcome that presents earlier than mortality in general, and muscle mass may be independently associated with mortality in men.

The SMI–mortality association, independent of HGS, has also been reported in a recent systematic review and meta-analysis.[37] Muscle mass is a crucial reservoir of amino acids and effector molecules, such as myokines and cytokines, which help in combating illness, infection, and wasting.[38] Therefore, it may be associated with a wide range of life-threatening adverse health effects, especially in older adults.[38] Moreover, our results may be attributable to sex-related differences in muscle mass and fat mass. Men had a greater muscle mass and wider distribution than women, whereas women had a greater fat mass and wider distribution than men. This may provide an opportunity to better capture the heterogeneous risk profiles of individuals. Specifically, older Japanese men and women in this study had substantially lower FMI and higher SMI than those in previously studied Western populations.[21] These findings may explain the significant impact of SMI in men and a lower FMI in women on mortality risk.

There are some limitations of this study. First, selection bias is a concern because our study participants were limited to individuals who had undergone check-ups. Second, women had a low mortality rate, and we could not analyse the association of sarcopenia parameters with cause-specific disability and mortality. Third, in our follow-up period, the possible influence of reverse causation cannot be completely excluded, compared with previous studies with long-term follow-up.[35] However, we believe that a 5.3-year follow-up period is reasonable because predictive ability declines over time.[39,40] Fourth, although we statistically adjusted many covariates, there may be factors that we have not considered, such as polypharmacy and potentially inappropriate medications, which affect sarcopenia and disability in older adults.[41] Fifth, although HGS is a simple and useful index of muscle strength, it should not be used as a sole measure of overall muscle strength, especially in men.[42] More plausible conclusions regarding the strength–mortality association in men may be drawn by defining muscle strength as quadriceps strength in future studies. Moreover, the low activity variable we used may be insufficient to adjust for the confounding effects of physical activity. Nevertheless, we believe that our results would not differ significantly even after adjusting for physical activity, because a previous study reported significant associations of low muscle strength with increased risk of all-cause mortality, independent of sedentary time and leisure-time physical activity.[18] Finally, although we did confirm that direct segmental multi-frequency bioelectrical impedance analysis has an acceptable accuracy,[25] it probably underestimated lean mass and overestimated fat mass among older Japanese individuals compared with the measurements with dual-energy X-ray absorptiometry. Systematic bias is another concern when comparing measured dual-energy X-ray absorptiometry values.

Despite these limitations, to our knowledge, this is the first study to report on the shapes of the associations of body composition, muscle strength, and physical performance with incident disability and mortality risks simultaneously. Using spline analyses rather than a categorical or linear approach, we were able to continuously show the HRs for disability and mortality of each measurement (*Figures* 1–4). We believe that this information is useful for screening high-risk individuals in clinical and public health settings. It should be noted that the associations of each measurement with disability and mortality risks are not necessarily linear, as depicted in these results.

In conclusion, disability risk was consistently more dependent on muscle strength (defined by HGS) and physical performance (defined by UGS) than body composition in both sexes, while mortality risk was also influenced by body composition, independent of muscle strength and physical performance. In particular, mortality risk in men was more dependent on muscle mass than muscle strength and physical performance, and mortality risk in women was influenced by lower fat mass along with muscle strength and physical performance. Although improving muscle strength and phys-

ical performance (rather than only increasing muscle mass) should be the first target for health promotion, it is also necessary to pay attention to body composition to extend life expectancy in older adults.

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Conflict of interest

The authors declare that they have no competing interests.

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Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

References

1. Rosenberg IH. Summary comments. *Am J Clin Nutr* 1989;**50**:1231–1233.
2. Baumgartner RN, Koehler KM, Gallagher D, Romero L, Heymsfield SB, Ross RR, et al. Epidemiology of sarcopenia among the elderly in New Mexico. *Am J Epidemiol* 1998;**147**:755–763.
3. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on Sarcopenia in Older People. *Age Ageing* 2010;**39**:412–423.
4. Muscaritoli M, Anker SD, Argiles J, Aversa Z, Bauer JM, Biolo G, et al. Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by Special Interest Groups (SIG) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics". *Clin Nutr* 2010;**29**:154–159.
5. Fielding RA, Vellas B, Evans WJ, Bhasin S, Morley JE, Newman AB, et al. Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International working group on sarcopenia. *J Am Med Dir Assoc* 2011;**12**:249–256.
6. Chen LK, Liu LK, Woo J, Assantachai P, Auyeung TW, Bahyah KS, et al. Sarcopenia in Asia: consensus report of the Asian working group for sarcopenia. *J Am Med Dir Assoc* 2014;**15**:95–101.
7. Studenski SA, Peters KW, Alley DE, Cawthon PM, McLean RR, Harris TB, et al. The FNIH sarcopenia project: rationale, study description, conference recommendations, and final estimates. *J Gerontol A Biol Sci Med Sci* 2014;**69**:547–558.
8. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyere O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing* 2019;**48**:16–31.
9. Chen LK, Woo J, Assantachai P, Auyeung TW, Chou MY, Iijima K, et al. Asian Working Group for Sarcopenia: 2019 consensus update on sarcopenia diagnosis and treatment. *J Am Med Dir Assoc* 2020;**21**:300–7.e2.
10. Bhasin S, Travison TG, Manini TM, Patel S, Pencina KM, Fielding RA, et al. Sarcopenia definition: the position statements of the sarcopenia definition and outcomes consortium. *J Am Geriatr Soc* 2020;**68**:1410–1418.
11. Clark BC, Manini TM. Sarcopenia =/= dynapenia. *J Gerontol A Biol Sci Med Sci* 2008;**63**:829–834.
12. Manini TM, Clark BC. Dynapenia and aging: an update. *J Gerontol A Biol Sci Med Sci* 2012;**67**:28–40.
13. Newman AB, Kupelian V, Visser M, Simonsick EM, Goodpaster BH, Kritchevsky SB, et al. Strength, but not muscle mass, is associated with mortality in the health, aging and body composition study cohort. *J Gerontol A Biol Sci Med Sci* 2006;**61**:72–77.
14. Visser M, Goodpaster BH, Kritchevsky SB, Newman AB, Nevitt M, Rubin SM, et al. Muscle mass, muscle strength, and muscle fat infiltration as predictors of incident mobility limitations in well-functioning older persons. *J Gerontol A Biol Sci Med Sci* 2005;**60**:324–333.
15. Baker JF, Long J, Leonard MB, Harris T, Delmonico MJ, Santanasto A, et al. Estimation of skeletal muscle mass relative to adiposity improves prediction of physical performance and incident disability. *J Gerontol A Biol Sci Med Sci* 2018;**73**:946–952.
16. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet* 2004;**363**:157–163.
17. Goodpaster BH, Park SW, Harris TB, Kritchevsky SB, Nevitt M, Schwartz AV, et al. The loss of skeletal muscle strength, mass, and quality in older adults: the health, aging and body composition study. *J Gerontol A Biol Sci Med Sci* 2006;**61**:1059–1064.
18. Li R, Xia J, Zhang XI, Gathirua-Mwangi WG, Guo J, Li Y, et al. Associations of muscle mass and strength with all-cause mortality among US older adults. *Med Sci Sports Exerc* 2018;**50**:458–467.
19. Marrie RA, Dawson NV, Garland A. Quantile regression and restricted cubic splines are useful for exploring relation-

ships between continuous variables. *J Clin Epidemiol* 2009;**62**:511–7.e1.
20. Tseng LA, Delmonico MJ, Visser M, Boudreau RM, Goodpaster BH, Schwartz AV, et al. Body composition explains sex differential in physical performance among older adults. *J Gerontol A Biol Sci Med Sci* 2014;**69**:93–100.
21. Seino S, Kitamura A, Abe T, Taniguchi Y, Yokoyama Y, Amano H, et al. Dose-response relationships between body composition indices and all-cause mortality in older Japanese adults. *J Am Med Dir Assoc* 2020;**21**:726–33.e4.
22. Kitamura A, Seino S, Abe T, Nofuji Y, Yokoyama Y, Amano H, et al. Sarcopenia: prevalence, associated factors, and the risk of mortality and disability in Japanese older adults. *J Cachexia Sarcopenia Muscle* 2021;**12**:30–38.
23. Taniguchi Y, Fujiwara Y, Murayama H, Yokota I, Matsuo E, Seino S, et al. Prospective study of trajectories of physical performance and mortality among community-dwelling older Japanese. *J Gerontol A Biol Sci Med Sci* 2016;**71**: 1492–1499.
24. Murayama H, Nishi M, Shimizu Y, Kim MJ, Yoshida H, Amano H, et al. The Hatoyama cohort study: design and profile of participants at baseline. *J Epidemiol* 2012;**22**: 551–558.
25. Kim M, Shinkai S, Murayama H, Mori S. Comparison of segmental multifrequency bioelectrical impedance analysis with dual-energy X-ray absorptiometry for the assessment of body composition in a community-dwelling older population. *Geriatr Gerontol Int* 2015;**15**:1013–1022.
26. VanItallie TB, Yang MU, Heymsfield SB, Funk RC, Boileau RA. Height-normalized indices of the body's fat-free mass and fat mass: potentially useful indicators of nutritional status. *Am J Clin Nutr* 1990;**52**: 953–959.
27. Seino S, Shinkai S, Fujiwara Y, Obuchi S, Yoshida H, Hirano H, et al. Reference values and age and sex differences in physical performance measures for community-dwelling older Japanese: a pooled analysis of six cohort studies. *PLoS ONE* 2014;**9**:e99487. https://doi.org/10.1371/journal.pone.0099487
28. Tsutsui T, Muramatsu N. Care-needs certification in the long-term care insurance system of Japan. *J Am Geriatr Soc* 2005;**53**: 522–527.
29. Tsutsui T, Muramatsu N. Japan's universal long-term care system reform of 2005: containing costs and realizing a vision. *J Am Geriatr Soc* 2007;**55**:1458–1463.
30. Chen T, Honda T, Chen S, Narazaki K, Kumagai S. Dose-response association between accelerometer-assessed physical activity and incidence of disability in older Japanese adults: a 6-year prospective study. *J Gerontol A Biol Sci Med Sci* 2020; **75**:1763–1770.
31. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, et al. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 2009;**53**: 982–992.
32. Burke WJ, Roccaforte WH, Wengel SP. The short form of the Geriatric Depression Scale: a comparison with the 30-item form. *J Geriatr Psychiatry Neurol* 1991;**4**: 173–178.
33. Folstein MF, Folstein SE, McHugh PR. Mini-mental state: a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;**12**: 189–198.
34. Cesari M, Rolland Y, Abellan Van Kan G, Bandinelli S, Vellas B, Ferrucci L. Sarcopenia-related parameters and incident disability in older persons: results from the "invecchiare in Chianti" study. *J Gerontol A Biol Sci Med Sci* 2015;**70**: 457–463.
35. Rolland Y, Gallini A, Cristini C, Schott AM, Blain H, Beauchet O, et al. Body-composition predictors of mortality in women aged ≥75 y: data from a large population-based cohort study with a 17-y follow-up. *Am J Clin Nutr* 2014;**100**:1352–1360.
36. Desquilbet L, Mariotti F. Dose-response analyses using restricted cubic spline functions in public health research. *Stat Med* 2010;**29**:1037–1057.
37. de Santana FM, Premaor MO, Tanigava NY, Pereira RMR. Low muscle mass in older adults and mortality: a systematic review and meta-analysis. *Exp Gerontol* 2021; **152**:111461. https://doi.org/10.1016/j.exger.2021.111461
38. Argiles JM, Campos N, Lopez-Pedrosa JM, Rueda R, Rodriguez-Manas L. Skeletal muscle regulates metabolism via interorgan crosstalk: roles in health and disease. *J Am Med Dir Assoc* 2016;**17**:789–796.
39. Thompson MQ, Theou O, Tucker GR, Adams RJ, Visvanathan R. Recurrent measurement of frailty is important for mortality prediction: findings from the North West Adelaide Health Study. *J Am Geriatr Soc* 2019;**67**:2311–2317.
40. Sato K, Kondo N, Hanazato M, Tsuji T, Kondo K. Potential causal effect of physical activity on reducing the risk of dementia: a 6-year cohort study from the Japan Gerontological Evaluation Study. *Int J Behav Nutr Phys Act* 2021;**18**:140. https://doi.org/10.1186/s12966-021-01212-w
41. König M, Spira D, Demuth I, Steinhagen-Thiessen E, Norman K. Polypharmacy as a risk factor for clinically relevant sarcopenia: results from the Berlin Aging Study II. *J Gerontol A Biol Sci Med Sci* 2017;**73**: 117–122.
42. Yeung SSY, Reijnierse EM, Trappenburg MC, Hogrel JY, McPhee JS, Piasecki M, et al. Handgrip strength cannot be assumed a proxy for overall muscle strength. *J Am Med Dir Assoc* 2018;**19**:703–709.
43. von Haehling S, Morley JE, Coats AJS, Anker SD. Ethical guidelines for publishing in the Journal of Cachexia, Sarcopenia and Muscle: update 2021. *J Cachexia Sarcopenia Muscle* 2021;**12**:2259–2261.