Geriatrics & Gerontology International — Medline Indexed
Geriatr Gerontol Int 2018; **18 (Suppl. 1)**: 28–44

GUIDELINE

Chapter 4 Treatment of sarcopenia

Hidenori Arai,[1] Hidetaka Wakabayashi,[2] Yoshihiro Yoshimura,[3] Minoru Yamada,[4] Hunkyung Kim[5] and Atsushi Harada[1]

[1]National Center for Geriatrics and Gerontology, Obu, [2]Department of Rehabilitation Medicine, Yokohama City University Medical Center, Yokohama, [3]Department of Rehabilitation Medicine, Kumamoto Rehabilitation Hospital, Kumamoto, [4]Department of Lifespan Developmental Sciences, Graduate School of Comprehensive Human Sciences, University of Tsukuba, and [5]Research Team for Promoting Independence of the Elderly, Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan

Keywords: diet, exercise, protein, resistance training, vitamin D.

CQ1: Can exercise intervention be effective for sarcopenia?

Statement

- **Exercise interventions can be effective for increasing appendicular skeletal muscle mass, knee extension muscle strength, normal gait speed and maximum gait speed in patients with sarcopenia, and therefore are recommended (evidence level: very low; recommendation level: weak).**

Explanation

Exercise interventions are generally well known to provide benefits for muscle strength and physical function. However, much remains unclear as to whether this same efficacy will also be shown in patients with sarcopenia. A meta-analysis of seven randomized clinical trials (RCT) was carried out on skeletal muscle mass data, the basic concept of sarcopenia.[1] Based on the results, most of the RCT examined included data showing improvement in muscle strength[2–6] and physical functions, such as gait,[3–5,7] whereas just three of these studies had data showing increased skeletal muscle mass.[2,4,5] However, these RCT analyzed primarily older individuals residing locally whose conditions were also complicated by frailty,[1] and whether the study conclusions can also be applied to older patients diagnosed with sarcopenia before any intervention is debatable. Therefore, focusing on RCT regarding patients with sarcopenia is necessary.

In the systematic review carried out for this clinical question (CQ; Fig. 1),[8] although RCT focusing on older patients who satisfied either the European Working group on Sarcopenia in Older People (EWGSOP) or Asian Working group for Sarcopenia (AWGS) diagnostic criteria for sarcopenia were targeted, not all of the RCT screened applied inclusion criteria requiring older patients diagnosed with sarcopenia based on either the EWGSOP or AWGS criteria, and as such, RCT included participants diagnosed with sarcopenia based on a combination of the amount of reduction in skeletal muscle mass and muscle strength/physical functions. Exercise interventions administered in three extracted RCT comprised a comprehensive training program, including 60-min resistance exercises carried out twice weekly for 3 months.[9–11] Comparison against the control group who underwent nutritional intervention or health education showed that after the comprehensive training program, the appendicular skeletal muscle mass, normal gait speed, maximum gait speed and knee extension muscle strength were 0.38 kg, 0.11 m/s, 0.26 m/s, 0.11 Nm/kg and 8.55 Nm, respectively, each showing improvement.[8] In contrast, no change in grip strength was observed as a result of the comprehensive training program.[8] It is necessary to consider that although participants in this study were not diagnosed with sarcopenia based on established diagnostic criteria, such as the EWGSOP and AWGS, they were diagnosed using data showing decreased skeletal muscle mass.

With regard to other exercise interventions, whole-body vibration training was found to be ineffective in improving the cross-sectional area of the quadriceps vastus medialis muscle and knee extension muscle strength compared with participants in the control group who did not engage in a training program.[12]

Based on the above results, undergoing exercise interventions for ≥3 months might help increase skeletal muscle mass, muscle strength and gait speed. However, one issue is that the criteria used for the diagnosis of sarcopenia before the intervention do not always match the most current established diagnostic criteria, and as such, numerous aspects of this topic remain at a

Correspondence: Dr. Hidenori Arai MD PhD, National Center for Geriatrics and Gerontology, 7-430 Morioka-cho, Obu City, Aichi Prefecture 474-8511, Japan. Email: harai@ncgg.go.jp

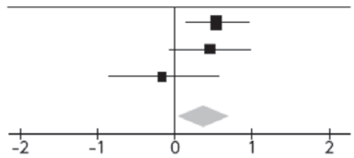
doi: 10.1111/ggi.13322 © 2018 Japan Geriatrics Society

1. Appendicular skeletal muscle volume (kg) after 3 months

Study or subgroup	Intervention group Mean	Intervention group SD	Intervention group Total	Control group Mean	Control group SD	Control group Total	Weight	Mean value difference IV, Random, 95% CI
Kim 2012	13.8986	1.4519	70	13.35	1.1154	74	44.8%	0.55 (0.12, 0.97)
Kim 2013	14.3173	1.4869	59	13.8404	1.3932	57	34.0%	0.48 (−0.05, 1.00)
Kim 2014	13	2.2356	70	13.1463	2.0338	67	21.2%	−0.15 (−0.86, 0.57)
Total (95% CI)			199			198	100.0%	0.38 (0.01, 0.74)

Heterogeneity: Tau^2=0.03; Chi^2=2.79, df=2(P=0.25); I^2=28%
Test for overall effect: Z=2.03(P=0.04)

Mean value difference IV, Random, 95% CI



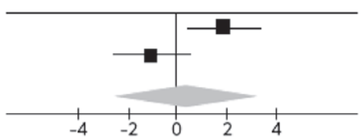
Favors control | Favors intervention

2. Grip strength (kg) after 3 months

Study or subgroup	Intervention group Mean	Intervention group SD	Intervention group Total	Control group Mean	Control group SD	Control group Total	Weight	Mean value difference IV, Random, 95% CI
Kim 2012	19.2944	4.5844	59	17.4195	3.2036	57	50.4%	1.87 (0.44, 3.31)
Kim 2013	19.94	4.5548	70	21.0015	4.5854	67	49.6%	−1.06 (−2.59, 0.47)
Total (95% CI)			129			124	100.0%	0.42 (−2.46, 3.30)

Heterogeneity: Tau^2=3.74; Chi^2=7.52, df=1(P=0.006); I^2=87%
Test for overall effect: Z=0.29(P=0.78)

Mean value difference IV, Random, 95% CI



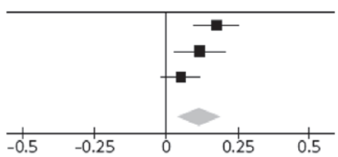
Favors control | Favors intervention

3. Normal gait speed (m/s) after 3 months

Study or subgroup	Intervention group Mean	Intervention group SD	Intervention group Total	Control group Mean	Control group SD	Control group Total	Weight	Mean value difference IV, Random, 95% CI
Kim 2012	1.466	0.2613	70	1.29	0.2169	74	32.8%	0.18 (0.10, 0.25)
Kim 2013	1.3649	0.2699	59	1.2498	0.1935	57	31.0%	0.12 (0.03, 0.20)
Kim 2016	1.2486	0.2048	70	1.2	0.1985	67	36.2%	0.05 (−0.02, 0.12)
Total (95% CI)			199			198	100.0%	0.11 (0.04, 0.19)

Heterogeneity: Tau^2=0.00; Chi^2=5.86, df=2(P=0.05); I^2=66%
Test for overall effect: Z=2.86(P=0.004)

Mean value difference IV, Random, 95% CI



Favors control | Favors intervention

Figure 1 Meta-analysis of randomized clinical trials (RCT) investigating the effects of exercise intervention to treat sarcopenia. Yoshimura *et al.*, J Am Med Dir Assoc 2017; 18: 553. e1–553. e16. © 2017 AMDA-The Society for Post-Acute and Long-Term Care Medicine, with permission from Elsevier.

very low evidence level. Further accumulation of clinical data will be necessary to clarify these issues.

CQ2: Can nutritional intervention be effective for sarcopenia?

Statement

- **Nutritional interventions focused on the intake of essential amino acids might improve knee extension muscle strength in patients with sarcopenia and are therefore recommended. However, the ability of this treatment approach to improve long-term outcomes is not yet clear (evidence level: very low; recommendation level: weak).**

Explanation

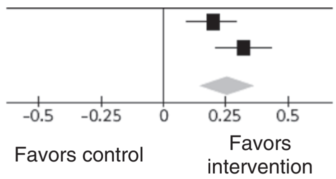
Nutritional interventions are strongly believed to offer benefits similar to those of exercise interventions in

4. Maximum gait speed (m/s) after 3 months

Study or subgroup	Intervention group Mean	Intervention group SD	Intervention group Total	Control group Mean	Control group SD	Control group Total	Weight	Mean value difference IV, Random, 95% CI
Kim 2012	1.9817	0.3257	70	1.78	0.3213	74	51.4%	0.20 (0.10, 0.31)
Kim 2013	2.0354	0.3539	59	1.71	0.2643	57	48.6%	0.33 (0.21, 0.44)
Total (95% CI)			129			131	100.0%	0.26 (0.14, 0.38)

Heterogeneity: Tau^2=0.00; Chi^2=2.44, df=1(P=0.12); I^2=59%
Test for overall effect: Z=4.23(P < 0.0001)

Mean value difference IV, Random, 95% CI

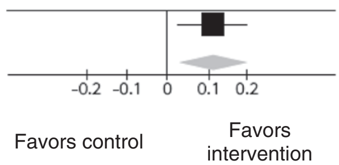


5. Knee extension strength (Nm/kg) after 3 months

Study or subgroup	Intervention group Mean	Intervention group SD	Intervention group Total	Control group Mean	Control group SD	Control group Total	Weight	Mean value difference IV, Random, 95% CI
Kim 2012	1.1837	0.2767	70	1.07	0.2629	74	100.0%	0.11 (0.03, 0.20)
Total (95% CI)			70			74	100.0%	0.11 (0.03, 0.20)

Heterogeneity: Not applicable
Test for overall effect: Z=2.52(P=0.01)

Mean value difference IV, Random, 95% CI

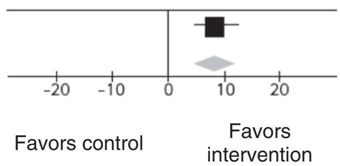


6. Knee extension strength (Nm) after 3 months

Study or subgroup	Intervention group Mean	Intervention group SD	Intervention group Total	Control group Mean	Control group SD	Control group Total	Weight	Mean value difference IV, Random, 95% CI
Kim 2012	49.789	11.3296	59	41.2425	9.7663	57	100.0%	8.55 (4.70, 12.39)
Total (95% CI)			59			57	100.0%	8.55 (4.70, 12.39)

Heterogeneity: Not applicable
Test for overall effect: Z=4.36(P< 0.0001)

Mean value difference IV, Random, 95% CI



7. Knee extension strength (N) after 3 months

Study or subgroup	Intervention group Mean	Intervention group SD	Intervention group Total	Control group Mean	Control group SD	Control group Total	Weight	Mean value difference IV, Random, 95% CI
Kim 2012	1.9817	0.3257	70	1.78	0.3213	74	51.4%	0.20 (0.10, 0.31)
Kim 2013	2.0354	0.3539	59	1.71	0.2643	57	48.6%	0.33 (0.21, 0.44)
Total (95% CI)			129			131	100.0%	0.26 (0.14, 0.38)

Heterogeneity: Tau^2=0.00; Chi^2=2.44, df=1(P=0.12); I^2=59%
Test for overall effect: Z=4.23(P <0.0001)

Mean value difference IV, Random, 95% CI

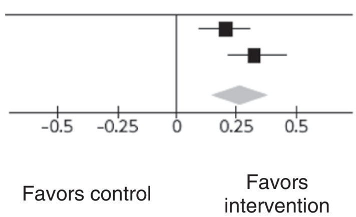


Figure 1 Continued.

regard to muscle strength and physical functions. However, numerous unclear points still remain regarding whether nutritional interventions also have beneficial effects in patients with sarcopenia. A meta-analysis examined 12 RCT evaluating skeletal muscle mass data, which is the basis for diagnosing sarcopenia.[1] This meta-analysis found that although improvement in physical functions, such as gait, was observed in three of

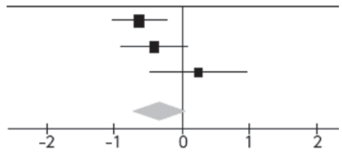
© 2018 Japan Geriatrics Society

1. Appendicular skeletal muscle volume (kg) after 3 months

Study or subgroup	Intervention group Mean	SD	Total	Control group Mean	SD	Total	Weight	Mean value difference IV, Random, 95% CI
Kim 2012	13.3064	1.3506	77	13.93	1.2188	78	41.0%	−0.62 (−1.03, −0.22)
Kim 2013	13.88	1.4345	64	14.28	1.4095	64	35.2%	−0.40 (−0.89, 0.09)
Kim 2016	13.1943	2.3407	70	12.9507	1.9144	69	23.9%	0.24 (−0.47, 0.95)
Total (95% CI)			211			211	100.0%	−0.34 (−0.78, 0.10)

Heterogeneity: Tau^2=0.08; Chi^2=4.32, df=2(P=0.12); I^2=54%
Test for overall effect: Z=1.50(P=0.13)

Mean value difference IV, Random, 95% CI

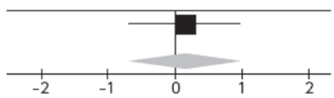


2. Appendicular skeletal muscle index (ASMI) (kg/m^2) after 4 months

Study or subgroup	Intervention group Mean	SD	Total	Control group Mean	SD	Total	Weight	Mean value difference IV, Random, 95% CI
Maltals 2012	9.45	0.907	16	9.3	1.1	10	100.0%	0.15 (−0.66, 0.96)
Total (95% CI)			16			10	100.0%	0.15 (−0.66, 0.96)

Heterogeneity: Not applicable
Test for overall effect: Z=0.36(P=0.72)

Mean value difference IV, Random, 95% CI

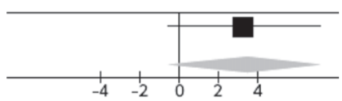


3. Fat-free mass (FFM) (kg) after 3 months

Study or subgroup	Intervention group Mean	SD	Total	Control group Mean	SD	Total	Weight	Mean value difference IV, Random, 95% CI
Zdzleblik 2015	61.1	6.88	26	57.8	7.46	27	100.0%	3.30 (−0.56, 7.16)
Total (95% CI)			26			27	100.0%	3.30 (−0.56, 7.16)

Heterogeneity: Not applicable
Test for overall effect: Z=1.67(P=0.09)

Mean value difference IV, Random, 95% CI



4. Grip strength (kg) after 3 months

Study or subgroup	Intervention group Mean	SD	Total	Control group Mean	SD	Total	Weight	Mean value difference IV, Random, 95% CI
Kim 2013	18.22	4.0066	64	18.5	4.1317	64	53.9%	−0.28 (−1.69, 1.13)
Kim 2016	20.2314	5.1559	70	20.6942	3.9421	69	46.1%	−0.46 (−1.99, 1.06)
Total (95% CI)			134			133	100.0%	−0.36 (−1.40, 0.67)

Heterogeneity: Tau^2=0.00; Chi^2=0.03, df=1(P=0.86); I^2=0%
Test for overall effect: Z=0.69(P=0.49)

Mean value difference IV, Random, 95% CI

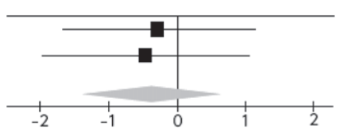


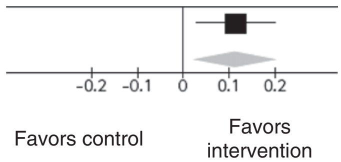
Figure 2 Meta-analysis of randomized clinical trials (RCT) investigating the effects of nutritional intervention to treat sarcopenia. Yoshimura *et al.*, J Am Med Dir Assoc 2017; 18: 553. e1–553. e16. © 2017 AMDA-The Society for Post-Acute and Long-Term Care Medicine, with permission from Elsevier.

5. Knee extension strength (Nm/kg) after 3 months

Study or subgroup	Intervention group Mean	Intervention group SD	Intervention group Total	Control group Mean	Control group SD	Control group Total	Weight	Mean value difference IV, Random, 95% CI
Kim 2012	1.1844	0.2725	77	1.07	0.2677	78	100.0%	0.11 (0.03, 0.20)
Total (95% CI)			77			78	100.0%	0.11 (0.03, 0.20)

Heterogeneity: Not applicable
Test for overall effect: Z=2.64(P=0.008)

Mean value difference IV, Random, 95% CI

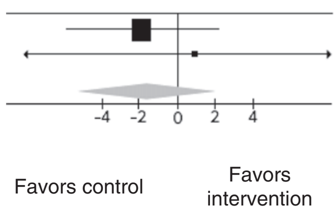


6. Knee extension strength (Nm) after 3 months

Study or subgroup	Intervention group Mean	Intervention group SD	Intervention group Total	Control group Mean	Control group SD	Control group Total	Weight	Mean value difference IV, Random, 95% CI
Kim 2013	44.635	10.0517	64	46.43	12.5674	64	93.5%	−1.80 (−5.74, 2.15)
Zdzleblik 2015	140	28.3	26	139	27.4	27	6.5%	1.00 (−14.00, 16.00)
Total (95% CI)			90			91	100.0%	−1.61 (−5.43, 2.20)

Heterogeneity: Tau^2=0.00; Chi^2=0.12, df=1(P=0.72); I^2=0%
Test for overall effect: Z=0.83(P=0.41)

Mean value difference IV, Random, 95% CI

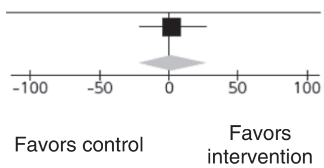


7. Knee extension strength (N) after 3 months

Study or subgroup	Intervention group Mean	Intervention group SD	Intervention group Total	Control group Mean	Control group SD	Control group Total	Weight	Mean value difference IV, Random, 95% CI
Kim 2016	205.4571	58.3368	70	203.3899	66.6866	69	100.0%	2.07 (−18.77, 22.91)
Total (95% CI)			70			69	100.0%	2.07 (−18.77, 22.91)

Heterogeneity: Not applicable
Test for overall effect: Z=0.19(P=0.85)

Mean value difference IV, Random, 95% CI



8. Normal gait speed (m/s) after 3 months

Study or subgroup	Intervention group Mean	Intervention group SD	Intervention group Total	Control group Mean	Control group SD	Control group Total	Weight	Mean value difference IV, Random, 95% CI
Kim 2012	1.3945	0.2416	77	1.36	0.2685	78	30.8%	0.03 (−0.05, 0.11)
Kim 2013	1.305	0.2245	64	1.31	0.2579	64	28.8%	−0.01 (−0.09, 0.08)
Kim 2016	1.2	0.1985	70	1.2507	0.2048	69	40.4%	−0.05 (−0.12, 0.02)
Total (95% CI)			211			211	100.0%	−0.01 (−0.06, 0.04)

Heterogeneity: Tau^2=0.00; Chi^2=2.59, df=2(P=0.27); I^2=23%
Test for overall effect: Z=0.44(P=0.66)

Mean value difference IV, Random, 95% CI

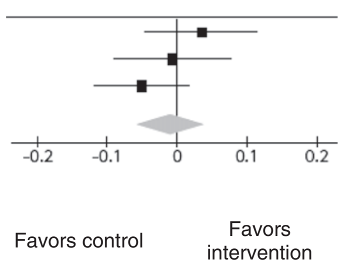


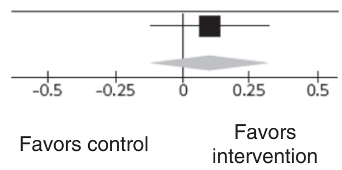
Figure 2 Continued.

these studies,[9,10,13] increases in skeletal muscle mass[14] and improvements in muscle strength[15] were observed in one study, respectively. In addition, these RCT primarily examined older individuals, including frail older adults.[1] As such, whether the conclusions reached as a result of these studies can also be applied to older

© 2018 Japan Geriatrics Society

9. Normal gait speed (m/s) after 4 months

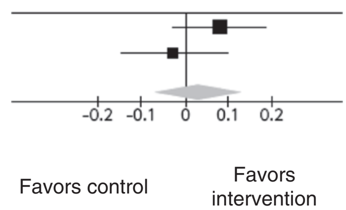
Study or subgroup	Intervention group			Control group			Weight	Mean value difference IV, Random, 95% CI	Mean value difference IV, Random, 95% CI
	Mean	**SD**	**Total**	**Mean**	**SD**	**Total**			
Kim 2012	1.5	0.2463	16	1.4	0.3	10	100.0%	0.10 (−0.12, 0.32)	
Total (95% CI)			16			10	100.0%	0.10 (−0.12, 0.32)	



Heterogeneity: Not applicable
Test for overall effect: Z=0.88(P=0.38)

10. Maximum gait speed (m/s) after 3 months

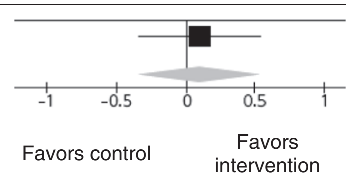
Study or subgroup	Intervention group			Control group			Weight	Mean value difference IV, Random, 95% CI	Mean value difference IV, Random, 95% CI
	Mean	**SD**	**Total**	**Mean**	**SD**	**Total**			
Kim 2012	1.92	0.3211	77	1.84	0.352	78	54.4%	0.08 (−0.03, 0.19)	
Kim 2013	1.86	0.3518	64	1.885	0.3547	64	45.6%	−0.02 (−0.15, 0.10)	
Total (95% CI)			141			142	100.0%	0.03 (−0.07, 0.13)	



Heterogeneity: Tau^2=0.00; Chi^2=1.61, df=1(P=0.20); I^2=38%
Test for overall effect: Z=0.61(P=0.54)

11. Maximum gait speed (m/s) after 4 months

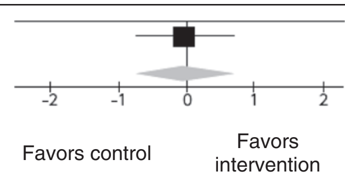
Study or subgroup	Intervention group			Control group			Weight	Mean value difference IV, Random, 95% CI	Mean value difference IV, Random, 95% CI
	Mean	**SD**	**Total**	**Mean**	**SD**	**Total**			
Maltals 2016	2	0.4698	16	1.9	0.6	10	100.0%	0.10 (−0.34, 0.54)	
Total (95% CI)			16			10	100.0%	0.10 (−0.34, 0.54)	



Heterogeneity: Not applicable
Test for overall effect: Z=0.45(P=0.65)

12. Timed Up and Go test performance (s) after 3 months

Study or subgroup	Intervention group			Control group			Weight	Mean value difference IV, Random, 95% CI	Mean value difference IV, Random, 95% CI
	Mean	**SD**	**Total**	**Mean**	**SD**	**Total**			
Kim 2013	7.905	1.972	64	7.955	1.9754	64	100.0%	−0.05 (−0.73, 0.63)	
Total (95% CI)			64			64	100.0%	−0.05 (−0.73, 0.63)	



Heterogeneity: Not applicable
Test for overall effect: Z=0.14(P=0.89)

Figure 2 Continued.

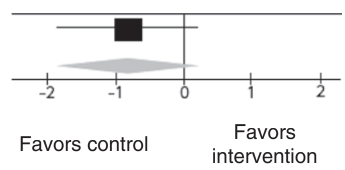
patients diagnosed with sarcopenia before intervention is debatable. Therefore, focusing on RCT examining older patients with sarcopenia was determined to be necessary.

The systematic review for this CQ examined five RCT (Fig. 2) focusing on older patients previously diagnosed with sarcopenia.[8] The nutritional interventions carried out in these studies included the administration of 3 g essential amino acids twice daily,[9] 540 mg tea catechin supplement daily,[10] 3 g essential amino acids and 540 mg tea catechin daily,[11] and 12 g protein and 7 g essential amino acids daily.[16]

As a nutritional intervention, essential amino acid supplementation was observed to be effective for improving knee extension muscle strength (0.11 Nm/

13. Timed up and go test performance (s) after 4 months

Study or subgroup	Intervention group Mean	SD	Total	Control group Mean	SD	Total	Weight	Mean value difference IV, Random, 95% CI	Mean value difference IV, Random, 95% CI
Maltals 2016	6.2	1.086 9	16	7	1.4	10	100.0%	−0.80 (−1.82, 0.22)	
Total (95% CI)			16			10	100.0%	−0.80 (−1.82, 0.22)	



Heterogeneity: Not applicable
Test for overall effect: Z=1.54(P=0.12)

Figure 2 Continued.

kg 3 months after).[9] However, no significant differences were observed with respect to skeletal muscle mass, fat-free mass (FFM), grip strength, knee extension muscle strength, gait speed or Timed Up and Go test performance,[7,17] which were examined in many combinations, including use of other nutritional supplementation methods. Considering that participants in these studies were diagnosed with sarcopenia based on the degree of decline in skeletal muscle mass rather than in accordance with established diagnostic criteria, such as the EWGSOP and AWGS, is necessary.

The results of the above studies showed that nutritional interventions extending for at least 3 months might contribute to improvement in muscle strength. However, further studies investigating whether such interventions also affect skeletal muscle mass and physical functions are required. Another concern is that the criteria used to diagnose sarcopenia before intervention do not always match the most current established diagnostic criteria, and as such numerous aspects of this topic remain at a very low evidence level. Further accumulation of clinical data will be necessary to clarify these issues.

CQ3: Can drug therapy be effective for sarcopenia?

Statement

- **Therapeutic drugs including selective androgen receptor modulators (SARM) are partially effective in improving sarcopenia, but no such drugs are currently approved in Japan (evidence level: very low; recommendation level: weak).**

Explanation

Changes in the endocrine environment accompanying aging, decreases in skeletal muscle mass and muscle weakness are closely related. The body of evidence regarding the efficacy of drug therapy as a treatment for sarcopenia is currently inadequate. However, some reports showed that skeletal muscle mass and muscle strength both can increase as a result androgen supplementation therapy, but the participants in these studies were men showing decreased gonadal function and postmenopausal women[18,19] rather than older patients with sarcopenia. This CQ will pay particular attention to the results of review articles[20] and studies verifying the ability of SARM to improve skeletal muscle mass and physical functions in healthy men and postmenopausal women.[21] As such, this CQ will assess whether drug therapies can be effective for increasing skeletal muscle mass, muscle strength and physical functions in older patients with sarcopenia through a review of the results of the existing literature published to date. Based on the results of a systematic review and meta-analysis carried out to verify the therapeutic effects of drugs, 1011 articles were extracted, but only one article regarding verification of the efficacy of drug therapy as a treatment for sarcopenia in older patients could be found (Fig. 3).[8]

In 2013, Papanicolaou *et al.*, carried out a randomized, double-blinded study in which 170 women aged >65 years with sarcopenia were assigned to either a group administered 50 mg SARM (MK-0773) or a placebo for 6 months, during which the participants were monitored with respect to changes in skeletal muscle mass and physical functional capacity.[22] All participants received a placebo 14 days before the start of the study intervention, after which the participants were randomly assigned to either the MK-0773 or placebo group. All participants were also administered protein and vitamin D throughout the study period. The participants were administered 25–35 g/day protein supplementation from the start of the intervention, and 2800–5600 IU/day vitamin D 14 days before the start of the intervention. Changes in lean body mass (LBM) after 3 months were 1.00 kg (95% CI 0.59–1.41) greater in the MK-0773 group compared with the placebo group. In addition, the change in appendicular LBM was 0.56 kg (95% CI 0.35–0.78) greater in the MK-0773 group compared with the placebo group. Furthermore, changes in LBM and appendicular LBM after 6 months in the MK-0773 group were greater than those in the

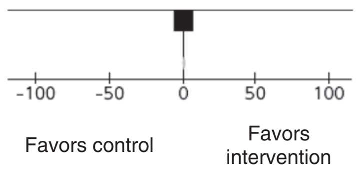
© 2018 Japan Geriatrics Society

1. Appendicular lean body mass (aLBM) (kg) after 6 months

Study or subgroup	Intervention group Mean	Intervention group SD	Intervention group Total	Control group Mean	Control group SD	Control group Total	Weight	Mean value difference IV, Random, 95% CI
Papanicolaou 2013	13.27	1.84	65	12.56	1.57	60	100.0%	0.71 (0.11, 1.31)
Total (95% CI)			65			60	100.0%	0.71 (0.11, 1.31)

Heterogeneity: Not applicable
Test for overall effect: Z=2.33(P=0.02)

Mean value difference IV, Random, 95% CI

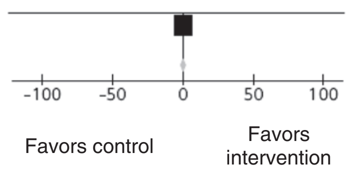


2. Lean body mass (LBM) (kg) after 6 months

Study or subgroup	Intervention group Mean	Intervention group SD	Intervention group Total	Control group Mean	Control group SD	Control group Total	Weight	Mean value difference IV, Random, 95% CI
Papanicolaou 2013	32.21	3.52	65	31.12	3.43	60	100.0%	1.09 (–0.13, 2.31)
Total (95% CI)			65			60	100.0%	1.09 (–0.13, 2.31)

Heterogeneity: Not applicable
Test for overall effect: Z=1.75(P=0.08)

Mean value difference IV, Random, 95% CI

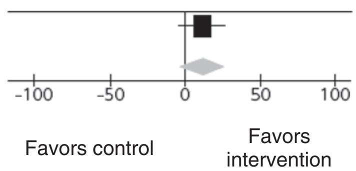


3. Bilateral leg press (lb) after 6 months

Study or subgroup	Intervention group Mean	Intervention group SD	Intervention group Total	Control group Mean	Control group SD	Control group Total	Weight	Mean value difference IV, Random, 95% CI
Papanicolaou 2013	77.88	46.58	66	66.75	38.76	63	100.0%	11.13 (–3.63, 25.89)
Total (95% CI)			66			63	100.0%	11.13 (–3.63, 25.89)

Heterogeneity: Not applicable
Test for overall effect: Z=1.48(P=0.14)

Mean value difference IV, Random, 95% CI



4. Stair-climbing power (W) after 6 months

Study or subgroup	Intervention group Mean	Intervention group SD	Intervention group Total	Control group Mean	Control group SD	Control group Total	Weight	Mean value difference IV, Random, 95% CI
Papanicolaou 2013	89.46	28.63	65	83.49	27.31	63	100.0%	5.97 (–3.72, 15.66)
Total (95% CI)			65			63	100.0%	5.97 (–3.72, 15.66)

Heterogeneity: Not applicable
Test for overall effect: Z=1.21(P=0.23)

Mean value difference IV, Random, 95% CI

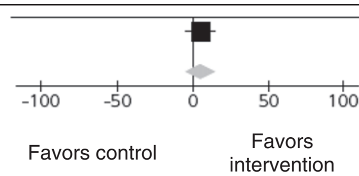


Figure 3 Meta-analysis of randomized clinical trials (RCT) investigating the effects of drug therapy to treat sarcopenia. Yoshimura *et al.*, J Am Med Dir Assoc 2017; 18: 553. e1–553. e16. © 2017 AMDA-The Society for Post-Acute and Long-Term Care Medicine, with permission from Elsevier.

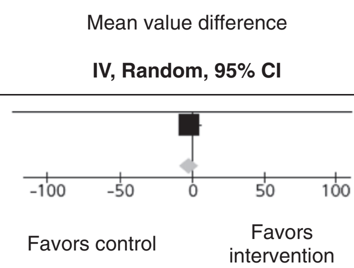
placebo group. However, leg press performance, gait speed and stair-climbing capacity increased in both groups, and no significant difference was observed between the MK-0773 and placebo groups with respect to these factors. As such, although significant changes in the LBM and appendicular LBM values were observed between the baseline and after 3 months, no significant increases were observed between the 3- and 6-month values.

Based on the above results, although increased skeletal muscle mass was observed as a therapeutic effect of drugs administered to older patients with sarcopenia, increased muscle strength or gait speed was not observed. No report verified the therapeutic effects of

5. Gait speed (cm/s) after 6 months

Study or subgroup	Intervention group Mean	SD	Total	Control group Mean	SD	Total	Weight	Mean value difference IV, Random, 95% CI
Papanicolaou 2013	75.39	18.55	66	77.12	17.63	63	100.0%	−1.73 (−7.97, 4.51)
Total (95% CI)			66			63	100.0%	−1.73 (−7.97, 4.51)

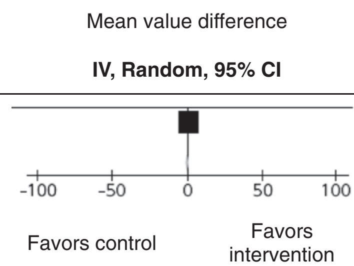
Heterogeneity: Not applicable
Test for overall effect: Z=0.54(P=0.59)



6. Short Physical Performance Battery (SPPB) total score after 6 months

Study or subgroup	Intervention group Mean	SD	Total	Control group Mean	SD	Total	Weight	Mean value difference IV, Random, 95% CI
Papanicolaou 2013	8.88	2.19	66	8.9	1.93	63	100.0%	−0.02 (−0.73, 0.69)
Total (95% CI)			66			63	100.0%	−0.02 (−0.73, 0.69)

Heterogeneity: Not applicable
Test for overall effect: Z=0.06(P=0.96)



7. Activity measure for post-acute care (AM-PAC) mobility score after 6 months

Study or subgroup	Intervention group Mean	SD	Total	Control group Mean	SD	Total	Weight	Mean value difference IV, Random, 95% CI
Papanicolaou 2013	62.31	6.27	65	61.51	5.46	63	100.0%	0.80 (−1.23, 2.83)
Total (95% CI)			65			63	100.0%	0.80 (−1.23, 2.83)

Heterogeneity: Not applicable
Test for overall effect: Z=0.77(P=0.44)

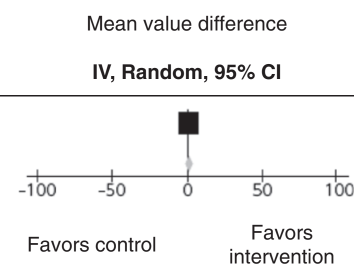


Figure 3 Continued

drugs in men with sarcopenia. Based on this background, the evidence level available regarding the therapeutic effects of drugs in older patients with sarcopenia is low, and no medications can currently be affirmatively recommended as treatments for sarcopenia. Large-scale interventions of participant populations, including men, will be required in the future.

CQ4: Can combined interventions be effective for sarcopenia?

Statement

- **Compared with singular interventions, combined interventions, including comprehensive exercise-based treatment interventions, such as resistance training and nutritional intervention, are effective for improving sarcopenia and are recommended. However, the ability of this approach to improve long-term outcomes is not yet clear (evidence level: very low; recommendation level: weak).**

Explanation

We screened 315 articles regarding combined intervention approaches. As a result of a systematic review[8] that meta-analyzed four articles (sample size 501) to verify the effects of combined interventions in three studies,[9–11] a subgroup analysis, including studies comparing a combined intervention group against an exercise intervention only group, or a combined intervention group against a nutritional intervention only group, was carried out. In addition, an RCT by Zdzieblik *et al.*, investigated older adults who engaged in 60-min resistance training using exercise machines

© 2018 Japan Geriatrics Society

thrice a week while receiving 15 g collagen peptide or a placebo for 3 months.[17] A subgroup meta-analysis incorporating these four RCT was carried out to compare the effects of: (i) exercise intervention alone versus a combination of nutrition and exercise interventions; and (ii) combined exercise and nutritional intervention versus nutritional intervention alone.

1) Comparison of exercise + nutrition versus exercise only

Although combined exercise + nutritional interventions tended to increase FFM after 3 months in the four RCT analyzed, no significant changes in appendicular skeletal muscle mass, grip strength, knee extension muscle strength or normal/maximum gait speed were observed (Fig. 4).[8]

2) Comparison of exercise + nutrition versus nutrition only

In three of the RCT analyzed, combined exercise + nutritional interventions were found to be effective for improving knee extension muscle strength after 3 months. However, no significant changes were observed with respect to appendicular skeletal muscle mass, grip strength or normal/maximum gait speed (Fig. 5).[8]

Although the nature of any additive effects of exercise and nutritional interventions could not be clarified through this systematic review because the participants were primarily older patients presenting with decreased skeletal muscle mass + grip strength or decreased gait speed, Rondanelli *et al.*, reported increased FFM and improved muscle strength in older patients with low skeletal muscle mass who were administered whey protein, essential amino acids and vitamin D supplementation for 12 weeks after all the participants had completed an exercise intervention.[23] Accordingly, a combination of exercise and nutrition was considered to form the foundation of any effective therapeutic intervention for sarcopenia. Furthermore, although not sarcopenia, the ability of combined exercise and nutritional interventions to improve muscle strength has also been shown in patients with chronic obstructive pulmonary disease (COPD),[24] frail older adults[6] and patients with osteoporosis.[25]

No additive effects were observed in patients with sarcopenia as a result of exercise + nutritional interventions in this systematic review, and further accumulation of evidence regarding the content of exercise and nutritional interventions is required.

CQ5: Are interventions for secondary sarcopenia effective as treatment for the primary disease?

Statement

- **Exercise is effective for increasing skeletal muscle mass and physical functions in patients with breast and prostate cancers (evidence level: very low; recommendation level: weak).**
- **Amino acid supplementation is effective for improving physical functions in patients with COPD (evidence level: very low; recommendation level: weak).**
- **Exercise can be expected to result in improved physical functions in patients with chronic kidney disease (CKD) (evidence level: very low; recommendation level: weak).**
- **Exercise and testosterone supplementation can be expected to result in improved physical functions in patients with chronic heart failure (evidence level: very low; recommendation level: weak).**
- **Testosterone supplementation can be expected to result in increased skeletal muscle mass in patients with osteoporosis (evidence level: very low; recommendation level: weak).**

Diseases leading to secondary sarcopenia include cancer, COPD, CKD, heart failure, osteoporosis and others. This assessment investigated whether improvement in the state of the primary disease was achieved following treatment interventions designed to address sarcopenia.

First, few reports currently described the results of clinical trial results investigating the impact of improving sarcopenia in conjunction with cancer treatment. Supplementation with vitamin D or β-hydroxy-β-methylbutyric acid in cancer patients is effective for increasing or preventing decreases in muscle mass,[26] whereas suitable amounts of exercise have been reported to potentially suppress loss of muscle mass during breast cancer treatment.[27] In addition, in an RCT investigating 57 patients with prostate cancer undergoing androgen suppression therapy for >2 months, the patients were divided into a resistance + aerobic exercise group (29 patients) and a usual care group (28 patients), and were observed over a 12-week period. As a result, patients in the exercise group showed significant increases in skeletal muscle mass, (whole body, lower extremities, upper extremities), increased muscle strength and gait function compared with the usual care group.[28]

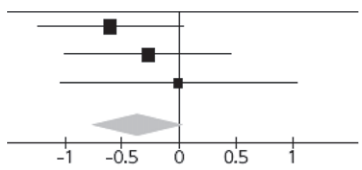
Respiratory rehabilitation and physical training to improve COPD have been shown to result in increases in bodyweight and skeletal muscle mass, as well as improved motor functions. In another study investigating the impact of amino acid supplementation, 32 patients aged >40 years with severe COPD complicated by sarcopenia were divided into a 4 g/b.i.d. amino acid group (16 patients) or a placebo group (16 patients), after which the degree of change in their conditions after 4 and 12 weeks was examined. As a result, compared with the placebo group, patients in the amino acid group showed a mean increase in bodyweight of 6 kg, a 3.6–kg increase

© 2018 Japan Geriatrics Society

1. Appendicular skeletal muscle volume (kg) after 3 months

Study or subgroup	Intervention group: Mean	SD	Total	Control group: Mean	SD	Total	Weight	Mean value difference IV, Random, 95% CI
Kim 2012	13.59	1.53	38	14.19	1.33	39	46.7%	-0.60 (−1.24, 0.04)
Kim 2013	14.18	1.41	32	14.45	1.57	32	35.9%	-0.27 (−1.00, 0.46)
Kim 2016	13	2.3	36	13	2.2	35	17.5%	0.00 (−1.05, 1.05)
Total (95% CI)			106			106	100.0%	−0.38 (−0.81, 0.06)

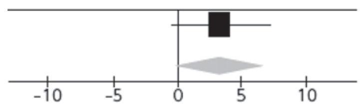
Heterogeneity: Tau^2=0.00; Chi^2=1.05, df=2(P=0.59); I^2=0%
Test for overall effect: Z=1.69(P=0.09)



2. Fat-free mass (FFM) (kg) after 3 months

Study or subgroup	Intervention group: Mean	SD	Total	Control group: Mean	SD	Total	Weight	Mean value difference IV, Random, 95% CI
Zdzieblik 2015	61.1	6.88	26	57.8	7.46	27	100.0%	3.30 (−0.56, 7.16)
Total (95% CI)			26			27	100.0%	3.30 (−0.56, 7.16)

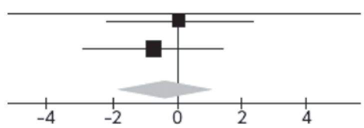
Heterogeneity: Not applicable
Test for overall effect: Z=1.67(P=0.09)



3. Grip strength (kg) after 3 months

Study or subgroup	Intervention group: Mean	SD	Total	Control group: Mean	SD	Total	Weight	Mean value difference IV, Random, 95% CI
Kim 2013	19.33	4.71	32	19.26	4.54	32	46.5%	0.07 (−2.20, 2.34)
Kim 2016	19.6	5.2	36	20.3	3.8	35	53.5%	−0.70 (−2.81, 1.41)
Total (95% CI)			68			67	100.0%	−0.34 (−1.89, 1.20)

Heterogeneity: Tau^2=0.00; Chi^2=0.24, df=1(P=0.63); I^2=0%
Test for overall effect: Z=0.43(P=0.66)



4. Knee extension strength (Nm/kg) after 3 months

Study or subgroup	Intervention group: Mean	SD	Total	Control group: Mean	SD	Total	Weight	Mean value difference IV, Random, 95% CI
Kim 2012	1.23	0.29	38	1.14	0.26	39	100.0%	0.09 (−0.03, 0.21)
Total (95% CI)			38			39	100.0%	0.09 (−0.03, 0.21)

Heterogeneity: Not applicable
Test for overall effect: Z=1.43(P=0.15)

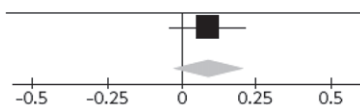


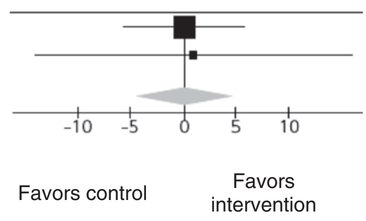
Figure 4 Meta-analysis of randomized clinical trials (RCT) comparing the effects of exercise + nutritional intervention against exercise intervention to treat sarcopenia. Yoshimura *et al.*, J Am Med Dir Assoc 2017; 18: 553. e1–553. e16. © 2017 AMDA-The Society for Post-Acute and Long-Term Care Medicine, with permission from Elsevier.

© 2018 Japan Geriatrics Society

5. Knee extension strength (Nm) after 3 months

Study or subgroup	Intervention group Mean	Intervention group SD	Intervention group Total	Control group Mean	Control group SD	Control group Total	Weight	Mean value difference IV, Random, 95% CI
Kim 2012	49.85	8.97	32	49.73	13.38	32	87.8%	0.12(−5.46, 5.70)
Zdzieblik 2015	140	28.3	26	139	27.4	27	12.2%	1.00 (−14.00, 16.00)
Total (95% CI)			58			59	100.0%	0.23(−5.00, 5.46)

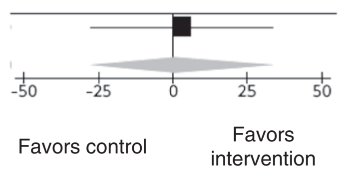
Heterogeneity: Tau^2=0.00; Chi^2=0.01, df=1(P=0.91); I^2=0%
Test for overall effect: Z=0.09(P=0.93)



6. Knee extension strength (N) after 3 months

Study or subgroup	Intervention group Mean	Intervention group SD	Intervention group Total	Control group Mean	Control group SD	Control group Total	Weight	Mean value difference IV, Random, 95% CI
Kim 2016	205.7	62.6	36	202.7	69.5	35	100.0%	3.00 (−27.79, 33.79)
Total (95% CI)			36			35	100.0%	3.00 (−27.79, 33.79)

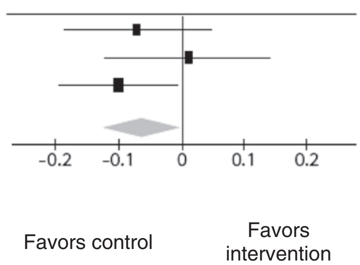
Heterogeneity: Not applicable
Test for overall effect: Z=0.19(P=0.85)



7. Normal gait speed (m/s) after 3 months

Study or subgroup	Intervention group Mean	Intervention group SD	Intervention group Total	Control group Mean	Control group SD	Control group Total	Weight	Mean value difference IV, Random, 95% CI
Kim 2012	1.43	0.29	38	1.5	0.23	39	29.8%	−0.07 (−0.19, 0.05)
Kim 2013	1.37	0.24	32	1.36	0.3	32	23.0%	0.01 (−0.12, 0.14)
Kim 2016	1.2	0.2	36	1.3	0.2	35	47.2%	−0.10 (−0.19, −0.01)
Total (95% CI)			106			106	100.0%	−0.07 (−0.13, −0.00)

Heterogeneity: Tau^2=0.00; Chi^2=1.77, df=2(P=0.41); I^2=0%
Test for overall effect: Z=2.02(P=0.04)



8. Maximum gait speed (m/s) after 3 months

Study or subgroup	Intervention group Mean	Intervention group SD	Intervention group Total	Control group Mean	Control group SD	Control group Total	Weight	Mean value difference IV, Random, 95% CI
Kim 2012	1.92	0.37	38	2.04	0.27	39	59.2%	−0.12 (−0.26, 0.02)
Kim 2013	2.01	0.39	32	2.06	0.32	32	40.8%	−0.05 (−0.22, 0.12)
Total (95% CI)			70			71	100.0%	−0.09 (−0.20, 0.02)

Heterogeneity: Tau^2=0.00; Chi^2=0.36, df=1(P=0.55); I^2=0%
Test for overall effect: Z=1.61(P=0.11)

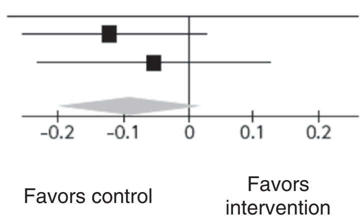


Figure 4 Continued.

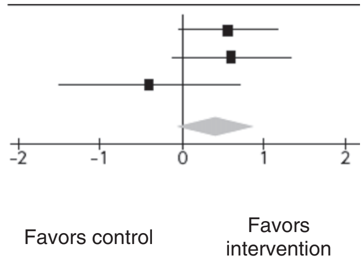
© 2018 Japan Geriatrics Society

1. Appendicular skeletal muscle volume (kg) after 3 months

Study or subgroup	Intervention group Mean	Intervention group SD	Intervention group Total	Control group Mean	Control group SD	Control group Total	Weight	Mean value difference IV, Random, 95% CI
Kim 2012	13.59	1.53	38	13.03	1.1	39	46.5%	0.56 (−0.04, 1.16)
Kim 2013	14.18	1.41	32	13.58	1.51	32	35.8%	0.60 (−0.12, 1.32)
Kim 2016	13	2.3	36	13.4	2.4	34	17.7%	−0.40 (−1.50, 0.70)
Total (95% CI)			106			105	100.0%	0.40 (−0.09, 0.90)

Heterogeneity: Tau^2=0.04; Chi^2=2.58, df=2(P=0.28); I^2=22%
Test for overall effect: Z=1.60(P=0.11)

Mean value difference IV, Random, 95% CI

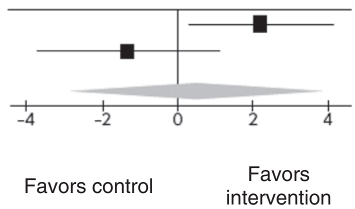


2. Grip strength (kg) after 3 months

Study or subgroup	Intervention group Mean	Intervention group SD	Intervention group Total	Control group Mean	Control group SD	Control group Total	Weight	Mean value difference IV, Random, 95% CI
Kim 2013	19.33	4.71	32	17.11	2.81	32	52.3%	2.22 (0.32, 4.12)
Kim 2016	19.6	5.2	36	20.9	5.1	34	47.7%	−1.30 (−3.71, 1.11)
Total (95% CI)			68			66	100.0%	0.54 (−2.90, 3.99)

Heterogeneity: Tau^2=4.97; Chi^2=5.04, df=1(P=0.02); I^2=80%
Test for overall effect: Z=0.31(P=0.76)

Mean value difference IV, Random, 95% CI

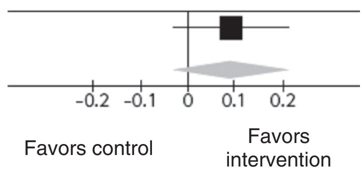


3. Knee extension strength (Nm/kg) after 3 months

Study or subgroup	Intervention group Mean	Intervention group SD	Intervention group Total	Control group Mean	Control group SD	Control group Total	Weight	Mean value difference IV, Random, 95% CI
Kim 2012	1.23	0.29	38	1.14	0.25	39	100.0%	0.09 (−0.03, 0.21)
Total (95% CI)			38			39	100.0%	0.09 (−0.03, 0.21)

Heterogeneity: Not applicable
Test for overall effect: Z=1.46(P=0.15)

Mean value difference IV, Random, 95% CI



4. Knee extension strength (Nm) after 3 months

Study or subgroup	Intervention group Mean	Intervention group SD	Intervention group Total	Control group Mean	Control group SD	Control group Total	Weight	Mean value difference IV, Random, 95% CI
Kim 2012	49.85	8.97	32	39.42	8.29	32	100.0%	10.43 (6.20, 14.66)
Total (95% CI)			32			32	100.0%	10.43 (6.20, 14.66)

Heterogeneity: Not applicable
Test for overall effect: Z=4.83(P < 0.00001)

Mean value difference IV, Random, 95% CI

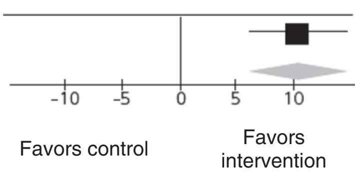


Figure 5 Meta-analysis of randomized clinical trials (RCT) comparing the effects of exercise + nutritional intervention against nutritional intervention to treat sarcopenia. Yoshimura Y, *et al.*, J Am Med Dir Assoc 2017; 18: 553. e1–553. e16. © 2017 AMDA-The Society for Post-Acute and Long-Term Care Medicine, with permission from Elsevier.

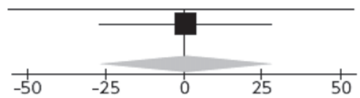
© 2018 Japan Geriatrics Society

5. Knee extension strength (N) after 3 months

Study or subgroup	Intervention group Mean	SD	Total	Control group Mean	SD	Total	Weight	Mean value difference IV, Random, 95% CI
Kim 2012	205.7	62.6	36	205.2	54.4	34	100.0%	0.50 (−26.93, 27.93)
Total (95% CI)			36			34	100.0%	0.50 (−26.93, 27.93)

Heterogeneity: Not applicable
Test for overall effect: Z=0.04(P=0.97)

Mean value difference IV, Random, 95% CI



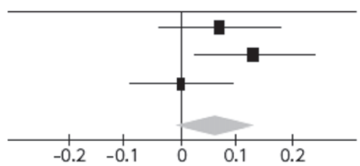
Favors control | Favors intervention

6. Normal gait speed (m/s) after 3 months

Study or subgroup	Intervention group Mean	SD	Total	Control group Mean	SD	Total	Weight	Mean value difference IV, Random, 95% CI
Kim 2012	1.43	0.29	38	1.36	0.18	39	31.1%	0.07 (−0.04, 0.18)
Kim 2013	1.37	0.24	32	1.24	0.19	32	31.9%	0.13 (0.02, 0.24)
Kim 2016	1.2	0.2	36	1.2	0.2	34	37.0%	0.00 (−0.09, 0.09)
Total (95% CI)			106			105	100.0%	0.06 (−0.01, 0.14)

Heterogeneity: $Tau^2=0.00$; $Chi^2=3.28$, df=2(P=0.19); $I^2=39\%$
Test for overall effect: Z=1.64(P=0.10)

Mean value difference IV, Random, 95% CI



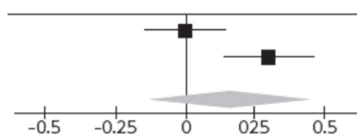
Favors control | Favors intervention

7. Maximum gait speed (m/s) after 3 months

Study or subgroup	Intervention group Mean	SD	Total	Control group Mean	SD	Total	Weight	Mean value difference IV, Random, 95% CI
Kim 2012	1.92	0.37	38	1.92	0.27	39	50.5%	0.00 (−0.14, 0.14)
Kim 2013	2.01	0.39	32	1.71	0.23	32	49.5%	0.30 (0.14, 0.46)
Total (95% CI)			70			71	100.0%	0.15 (−0.15, 0.44)

Heterogeneity: $Tau^2=0.04$; $Chi^2=7.58$, df=1(P=0.006); $I^2=87\%$
Test for overall effect: Z=0.99(P=0.32)

Mean value difference IV, Random, 95% CI



Favors control | Favors intervention

Figure 5 Continued.

in FFM, increased physical activity, improved cognitive function and improved overall health.[29]

Sarcopenia readily complicates CKD cases, and the prevalence of sarcopenia increases as the severity of CKD progresses to higher stages.[30] Exercise, and amino acid and vitamin D supplementation are both effective for improving inactivity and sarcopenia symptoms in patients with CKD.[31] In support of this observation, based on the results of another study in which 119 patients with stage 3 or 4 CKD were randomly selected and placed into a group undergoing exercise training (65 patients) or a usual care group (54 patients), and then followed for 12 weeks, the performance on the 6-min walk test improved by 19% in the exercise training group, whereas the performance decreased by 10% ($P < 0.001$) in the usual care group. In addition, the performance on the chair-stand test improved by 29% and 0.7% in the exercise training and usual care groups, respectively ($P < 0.001$). These results suggested that the exercise program was effective for improving the physical capacities and QOL of patients with CKD.[32]

Restriction of physical activity due to diminished cardiac function in patients with chronic heart failure can result in decreased muscle mass and muscle weakness, and sarcopenia occurs as a complication in

© 2018 Japan Geriatrics Society

approximately 20% of older patients with chronic heart failure.[33] Although nutritional supplementation, exercise and hormone replacement therapy have been proposed as methods for improving sarcopenia and diminished cardiac function,[34] others have highlighted the effect of a high-protein diet and/or amino acid supplementation to cause weight gain in patients with chronic heart failure,[35] whereas exercise training has been shown to help reduce myostatin and improve aerobic capacity.[36,37] Although inadequate testosterone in patients with chronic heart failure has been associated with the onset of muscle weakness, such patients have shown improved gait functions and increased muscle strength as a result of testosterone supplementation.[38] Although similar effects have been reported with regard to supplementation with human growth hormone, ghrelin and vitamin D, there is currently insufficient evidence regarding the effects of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and β-blockers in patients with sarcopenia.

Osteoporosis is strongly associated with decreases in muscle mass and muscle strength. In a study of 131 men (mean age 77.1 ± 7.6 years) with a history of bone fractures, low bone density and low blood testosterone level, the participants were divided into either a group administered 5 mg/day testosterone supplementation or a placebo group, and were then observed for 12–24 months. As a result, femoral cervical and lumbar bone densities increased by 1.4% and 3.2%, respectively, in the testosterone-supplemented group. In addition, although muscle mass increased and body fat decreased in the testosterone-supplemented group, no differences in exercise capacity were observed compared with the placebo group.[39] Furthermore, in another study in which 5 mg/day of alendronate and 0.5 μg/day of calcitriol were administered for 6 months to 38 women (mean age 56.0 ± 8.00 years) with decreased bone density, interleukin-6 levels, lumbar vertebral bone density and grip strength decreased by 56.5%, 2.62% and 33.5%, respectively. These findings clearly show that treatment with 5 mg/day of alendronate and calcitriol is effective for suppressing bone loss and increasing skeletal muscle mass in women presenting with reduced bone density.[40]

See Figures S1–S4 for literature flowchart.

Disclosure statement

In the Sarcopenia clinical practice guidelines 2017 edition preparation committee, regarding the economic relationship between the committee members and the companies involved in sarcopenic diseases and sarcopenic diseases, each member gave declarations of the conflict of interest status in the past 3 years based on the following criteria. Remuneration of officers and advisory positions (¥ one million or more annually paid by a single company/organization), the possession of shares and the profit obtained from the stock (¥ one million or more of annual profit from one company or 5% or more of the total shares of the company), a fee paid as a royalty fee (one patent royalty of ¥ one million or more per year), a lecture fee (the annual sum total of ¥500 000 or more from one company/organization), manuscript (manuscript fee, daily allowance paid by one company/organization totaling more than ¥500 000), research expenses (total amount paid for one clinical study ¥ one million yen or more per year), donation (¥ one million or more per year by one company/organization), affiliation to a donated fund laboratory provided by a company and so on (if affiliated to the department), and other remuneration (an annual total of ¥50 000 or more rewards, such as gifts or trip unrelated to the studies provided by company/organization). All members of the committee are responsible for the contents of "Sarcopenia clinical practice guidelines 2017" as medical or medical specialists or specialists of sarcopenic diseases and related diseases, to ensure scientific and medical fairness and appropriateness, to extend the healthy lifespan of the target patient, and to improve quality of life. Regarding the treatment of conflicts of interest, it was in accordance with the Committee on Conflicts of Interest of Japan Medical Association "Guidelines on COI Management of Clinical Studies." The company names declared are as follows (the applicable period is 1 January 2014 to 31 December 2016). It does not include publishers and organizations in a neutral position.

Record

Asahi Kasei Pharma Corporation, Astellas Pharma Inc., AstraZeneca K.K., ALCARE Co., Ltd.,Inter Reha Co., Ltd., Eisai Co., Ltd., MSD K.K., Otsuka Pharmaceutical Co., Ltd., ONO PHARMACEUTICAL CO., LTD., Kao Corporation, Kyowa Hakko Kirin CO., LTD., CLINICO CO., LTD., Kuredoru, Kowa Pharmaceutical Co.Ltd., SHIONOGI & CO., LTD., Sucampo Pharma, LLC, DAIICHI SANKYO COMPANY, LIMITED, Taisho Toyama Pharmaceutical Co., Ltd., Sumitomo Dainippon Pharma Co., Ltd., Takeda Pharmaceutical Company Limited., Mitsubishi Tanabe Pharma Corporation, Chugai Pharmaceutical Co., Ltd., TSUKUI CORPORATION, TSUMURA & CO., TEIJIN PHARMA LIMITED., TOYOTA MOTOR CORPORATION, Eli Lilly Japan K.K., Boehringer Ingelheim, Nestle Japan Ltd., Novartis International AG, Bayer Yakuhin, Ltd., Pfizer Japan Inc., Bristol-Myers Squibb Company, HOYA CORPORATION, and MOCHIDA PHARMACEUTICAL.

© 2018 Japan Geriatrics Society

References

1 Cruz-Jentoft AJ, Landi F, Schneider SM *et al*. Prevalence of and interventions for sarcopenia in ageing adults: a systematic review. Report of the International Sarcopenia Initiative (EWGSOP and IWGS). *Age Ageing* 2014; **43**: 748–759.

2 Binder EF, Yarasheski KE, Steger-May K *et al*. Effects of progressive resistance training on body composition in frail older adults: results of a randomized, controlled trial. *J Gerontol A Biol Sci Med Sci* 2005; **60**: 1425–1431.

3 Bunout D, Barrera G, de la Maza P *et al*. The impact of nutritional supplementation and resistance training on the health functioning of free-living Chilean elders: results of 18 months of follow-up. *J Nutr* 2001; **131**: 2441S–2446S.

4 Suetta C, Andersen JL, Dalgas U *et al*. Resistance training induces qualitative changes in muscle morphology, muscle architecture, and muscle function in elderly postoperative patients. *J Appl Physiol* 2008; **105**: 180–186.

5 Kemmler W, von Stengel S, Engelke K, Häberle L, Mayhew JL, Kalender WA. Exercise, body composition, and functional ability a randomized controlled trial. *Am J Prev Med* 2010; **38**: 279–287.

6 Rydwik E, Lammes E, Frändin K, Akner G. Effects of a physical and nutritional intervention program for frail elderly individuals over age 75: a randomized controlled pilot treatment trial. *Aging Clin Exp Res* 2008; **20**: 159–170.

7 Bonnefoy M, Cornu C, Normand S *et al*. The effects of exercise and protein-energy supplements on body composition and muscle function in frail elderly individuals: a long-term controlled randomised study. *Br J Nutr* 2003; **89**: 731–739.

8 Yoshimura Y, Wakabayashi H, Yamada M, Kim H, Harada A, Arai H. Interventions for treating sarcopenia: a systematic review and meta-analysis of randomized controlled studies. *J Am Med Dir Assoc* 2017; **18**: 553.e1–553.e16.

9 Kim HK, Suzuki T, Saito K *et al*. Effects of exercise and amino acid supplementation on body composition and physical function in community-dwelling elderly Japanese sarcopenic women: a randomized controlled trial. *J Am Geriatr Soc* 2012; **60**: 16–23.

10 Kim H, Suzuki T, Saito K *et al*. Effects of exercise and tea catechins on muscle mass, strength and walking ability in community-dwelling elderly Japanese sarcopenic women: a randomized controlled trial. *Geriatr Gerontol Int* 2013; **13**: 458–465.

11 Kim H, Kim M, Kojima N *et al*. Exercise and nutritional supplementation on community-dwelling elderly Japanese women with sarcopenic obesity: a randomized controlled trial. *J Am Med Dir Assoc* 2016; **17**: 1011–1019.

12 Wei N, Pang MY, Ng SS, Ng GY. Optimal frequency/ time combination of whole-body vibration training for improving muscle size and strength of individuals with age-related muscle loss (sarcopenia): a randomized controlled trial. *Geriatr Gerontol Int* 2017; **17**: 1412–1420.

13 Tieland M, van de Rest O, Dirks ML *et al*. Protein supplementation improves physical performance in frail elderly individuals: a randomized, double-blind, placebo-controlled trial. *J Am Med Dir Assoc* 2012; **13**: 720–726.

14 Flakoll P, Sharp R, Baier S, Levenhagen D, Carr C, Nissen S. Effect of betahydroxy-beta-methylbutyrate, arginine, and lysine supplementation on strength, functionality, body composition, and protein metabolism in elderly women. *Nutrition* 2004; **20**: 445–451.

15 Tieland M, Dirks ML, van der Zwaluw N *et al*. Protein supplementation increases muscle mass gain during prolonged resistance-type exercise training in frail elderly individuals: a randomized, double-blind, placebo-controlled trial. *J Am Med Dir Assoc* 2012; **13**: 713–719.

16 Maltais ML, Ladouceur JP, Dionne IJ. The effect of resistance training and different sources of post-exercise protein supplementation on muscle mass and physical capacity in sarcopenic elderly men. *J Strength Cond Res* 2016; **30**: 1680–1687.

17 Zdzieblik D, Oesser S, Baumstark MW, Gollhofer A, König D. Collagen peptide supplementation in combination with resistance training improves body composition and increases muscle strength in elderly sarcopenic men: a randomised controlled trial. *Br J Nutr* 2015; **114**: 1237–1245.

18 Dobs AS, Nguyen T, Pace C, Roberts CP. Differential effects of oral estrogen versus oral estrogen androgen replacement therapy on body composition in postmenopausal women. *J Clin Endocrinol Metab* 2002; **87**: 1509–1516.

19 Wang C, Cunningham G, Dobs A *et al*. Long-term testosterone gel (AndroGel) treatment maintains beneficial effects on sexual function and mood, lean and fat mass, and bone mineral density in hypogonadal men. *J Clin Endocrinol Metab* 2004; **89**: 2085–2098.

20 Bhasin S, Jasuja R. Selective androgen receptor modulators as function promoting therapies. *Curr Opin Clin Nutr Metab Care* 2009; **12**: 232–240.

21 Dalton JT, Barnette KG, Bohl CE *et al*. The selective androgen receptor modulator GTx-024 (enobosarm) improves lean body mass and physical function in healthy elderly men and postmenopausal women: results of a double-blind, placebo-controlled phase II trial. *J Cachexia Sarcopenia Muscle* 2011; **2**: 153–161.

22 Papanicolaou DA, Ather SN, Zhu H *et al*. A phase IIA randomized, placebo-controlled clinical trial to study the efficacy and safety of the selective androgen receptor modulator (SARM), MK-0773 in female participants with sarcopenia. *J Nutr Health Aging* 2013; **17**: 533–543.

23 Rondanelli M, Klersy C, Terracol G *et al*. Whey protein, amino acids, and vitamin D supplementation with physical activity increases fat-free mass and strength, functionality, and quality of life and decreases inflammation in sarcopenic elderly. *Am J Clin Nutr* 2016; **103**: 830–840.

24 Sugawara K, Takahashi H, Kasai C *et al*. Effects of nutritional supplementation combined with low-intensity exercise in malnourished patients with COPD. *Respir Med* 2010; **104**: 1883–1889.

25 Swanenburg J, de Bruin ED, Stauffacher M, Mulder T, Uebelhart D. Effects of exercise and nutrition on postural balance and risk of falling in elderly individuals with decreased bone mineral density: randomized controlled trial pilot study. *Clin Rehabil* 2007; **21**: 523–534.

26 Mochamat H, Cuhls M, Marinova S *et al*. A systematic review on the role of vitamins, minerals, proteins, and other supplements for the treatment of cachexia in cancer: a European Palliative Care Research Centre cachexia project. *J Cachexia Sarcopenia Muscle* 2017; **8**: 25–39.

27 Hojan K, Milecki P, Molińska-Glura M, Roszak A, Leszczyński P. Effect of physical activity on bone strength and body composition in breast cancer premenopausal women during endocrine therapy. *Eur J Phys Rehabil Med* 2013; **49**: 331–339.

28 Galvão DA, Taaffe DR, Spry N, Joseph D, Newton RU. Combined resistance and aerobic exercise program reverses muscle loss in men undergoing androgen suppression therapy for prostate cancer without bone metastases: a randomized controlled trial. *J Clin Oncol* 2010; **28**: 340–347.

© 2018 Japan Geriatrics Society

29 Dal Negro RW, Aquilani R, Bertacco S, Boschi F, Micheletto C, Tognella S. Comprehensive effects of supplemented essential amino acids in patients with severe COPD and sarcopenia. *Monaldi Arch Chest Dis* 2010; **73**: 25–33.
30 Moon SJ, Kim TH, Yoon SY, Chung JH, Hwang HJ. Relationship between stage of chronic kidney disease and sarcopenia in Korean aged 40 years and older using the Korea National Health and Nutrition Examination Surveys (KNHANES IV- 2, 3, and V- 1, 2), 2008–2011. *PLoS One* 2015; **10**: e0130740.
31 Hirai K, Ookawara S, MY. Sarcopenia and physical inactivity in patients with chronic kidney disease. *Nephrourol Mon* 2016; **8**: e37443.
32 Rossi AP, Burris DD, Lucas FL, Crocker GA, Wasserman JC. Effects of a renal rehabilitation exercise program in patients with CKD: a randomized, controlled trial. *Clin J Am Soc Nephrol* 2014; **9**: 2052–2058.
33 Fülster S, Tacke M, Sandek A *et al.* Muscle wasting in patients with chronic heart failure: results from the studies investigating comorbidities aggravating heart failure (SICA-HF). *Eur Heart J* 2013; **34**: 512–519.
34 Collamati A, Marzetti E, Calvani R *et al.* Sarcopenia in heart failure: mechanisms and therapeutic strategies. *J Geriatr Cardiol* 2016; **13**: 615–624.
35 Rozentryt P, von Haehling S, Lainscak M *et al.* The effects of a high-caloric protein-rich oral nutritional supplement in patients with chronic heart failure and cachexia on quality of life, body composition, and inflammation markers: a randomized, double-blind pilot study. *J Cachexia Sarcopenia Muscle* 2010; **1**: 35–42.
36 Lenk K, Erbs S, Höllriegel R *et al.* Exercise training leads to a reduction of elevated myostatin levels in patients with chronic heart failure. *Eur J Prev Cardiol* 2012; **19**: 404–411.
37 Cunha TF, Bacurau AV, Moreira JB *et al.* Exercise training prevents oxidative stress and ubiquitin-proteasome system overactivity and reverse skeletal muscle atrophy in heart failure. *PLoS One* 2012; **7**: e41701.
38 Caminiti G, Volterrani M, Iellamo F *et al.* Effect of long-acting testosterone treatment on functional exercise capacity, skeletal muscle performance, insulin resistance, and baroreflex sensitivity in elderly patients with chronic heart failure a double-blind, placebo-controlled, randomized study. *J Am Coll Cardiol* 2009; **54**: 919–927.
39 Kenny AM, Kleppinger A, Annis K *et al.* Effects of transdermal testosterone on bone and muscle in older men with low bioavailable testosterone levels, low bone mass, and physical frailty. *J Am Geriatr Soc* 2010; **58**: 1134–1143.
40 Park JH, Park KH, Cho S *et al.* Concomitant increase in muscle strength and bone mineral density with decreasing IL- 6 levels after combination therapy with alendronate and calcitriol in postmenopausal women. *Menopause* 2013; **20**: 747–753.

Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website: .

Figure S1 Process flow for selection of literature sources for the Chapter 4-CQ1 systematic review.
Figure S2 Process flow for selection of literature sources for the Chapter 4-CQ2 systematic review.
Figure S3 Process flow for selection of literature sources for the Chapter 4-CQ3 systematic review.
Figure S4 Process flow for selection of literature sources for the Chapter 4-CQ4 systematic review.

© 2018 Japan Geriatrics Society