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Original Research

Effects of Beta-Hydroxy-Beta-Methylbutyrate Supplementation on Older Adults with Sarcopenia: A Randomized, Double-Blind, Placebo-Controlled Study

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Abstract

OBJECTIVES: Sarcopenia is recognized as a major public health concern because of its association with several adverse health events. Beta-hydroxy-beta-methylbutyrate (HMB) supplementation reportedly delays the loss of muscle mass and function; however, the effect of HMB on sarcopenia remains inconclusive. We aimed to evaluate the impact of HMB intervention on muscle strength, physical performance, body compositions, and inflammatory factors in older adults with sarcopenia.

DESIGN: Randomized, double-blind, placebo-controlled trial.

SETTING AND PARTICIPANTS: This study included subjects aged ≥60 years with sarcopenia which were assigned to the HMB group (HMBG, n=18) and the placebo group (PG, n=16).

INTERVENTION: The HMBG and PG were supplied with HMB and placebo products twice daily for 12 weeks, and both received resistance exercise training twice a week in 12 weeks.

MEASUREMENTS: Hand grip strength was selected as the primary outcome; gait speed, five-time chair stand test, body composition and inflammatory indicators were selected as the secondary outcomes. The differences in changes from baseline between the two groups were analyzed using the analysis of covariance(ANCOVA).

RESULTS: After the 12-week intervention, the HMBG demonstrated significantly greater improvements in handgrip strength (4.61(95%CI:2.93,6.28) kg, P<0.001), gait speed (0.11(95%CI:0.02,0.20)m/s, P=0.014), five-time chair stand test (-3.65 (95%CI:-5.72, -1.58)s, P=0.001), muscle quality (2.47(95%CI:1.15,3.80),$kg \cdot kg^{-1}$ P=0.001) and tumor necrosis factor-like weak inducer of apoptosis (-15.23(95%CI:-29.80,-0.66)pmol/mL, P=0.041) compared with the PG; no significant differences in skeletal muscle mass, skeletal muscle index, and other body composition parameters were found between the two groups.

CONCLUSION: In older adults with sarcopenia, HMB significantly enhance the effect of resistance exercise training on muscle strength, physical performance, muscle quality, and reduced inflammatory factors. Therefore, HMB supplementation could be an effective treatment for sarcorpenia. The trial protocol was registered at http://www.chictr.org.cn/showproj.aspx?proj=47571 as ChiCTR2000028778.

Key words: β-hydroxy-β-methylbutyrate, sarcopenia, aging, randomized controlled trial.

Introduction

Sarcopenia is a geriatric syndrome characterized by a generalized and progressive loss of muscle mass, muscle strength, and function with a risk of adverse health outcomes including falls, fractures, disability, and mortality (1). The current prevalence of sarcopenia in the older Asian population ranges from 6.8–25.7%, which presents a major public health problem that places a heavy burden on healthcare systems in an aging society (2). Thus, effective interventions are needed to prevent or delay sarcopenia.

Nutritional supplementation, especially beta-hydroxy-beta-methylbutyrate (HMB), a metabolite of leucine, which is an essential branched-chain amino acid with an anabolic role in the muscles (3), has been demonstrated to be an efficient intervention to improve muscle mass and function (4-6). The main mechanisms of the positive effect of HMB on muscles are as follows: increasing protein synthesis by stimulating the target of rapamycin (mTOR) signaling pathway leading to myogenic cell proliferation, and increasing serum concentrations of IGF-1; decreasing protein breakdown by downregulating the catabolic signaling pathways including ubiquitin-proteasome and autophagy-lysosome systems; enhancing muscle repair by increasing proliferation of satellite cells and decreasing inflammatory factors; and improving aerobic capacity by increasing mitochondrial biogenesis and fat oxidation (7, 8). Previous studies have indicated that the concentration of plasma HMB is positively associated with muscle mass and strength regardless of an older person's health status (9-11). However, in skeletal muscle, only 5–10% of α-ketoisocaproic acid (KIC) synthesized from leucine is transmitted to the liver and converted to HMB by the cytosolic enzyme KIC dioxygenase (5). Moreover, HMB and KIC dioxygenase levels in the plasma are inversely correlated with age (11, 12). These findings strongly support the rationale for HMB supplementation in older adults. Additionally, resistance exercise training (RET) is well defined as an effective regimen for building up strength as well as preventing muscle atrophy and weakness (13). However, RET probably induces fatigue, muscular injury, inflammatory reaction, and exercise-induced proteolysis (3), all of which are relieved by HMB (7, 14).

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Previous literature suggests that nutritional supplementation containing HMB can produce benefits in improving muscle mass, muscle strength and physical performance (15-17). Yet, there are few studies regarding the effect of HMB supplementation on older adults based on RET (18, 19), especially those with sarcopenia (20), and the results of these studies are conflicting (21). Also, the intervention products contained HMB as well as other ingredients such as other amino acids, protein, vitamin D, and vitamin C (16-20); this limits the ability to determine the direct and independent impact of HMB.

Therefore, this randomized, double-blind, placebo-controlled study aimed to evaluate whether HMB supplementation can improve muscle strength, function, and body composition in older adults with sarcopenia.

Materials and Methods

Study design and participants

This was a 12-week, randomized, double-blind, placebo-controlled trial conducted in Luzhou City, Sichuan Province, China. We launched a survey to screen for sarcopenia in older adults aged ≥60 years from the Lianxi, Chuxinyuan, Yutang, and Danxia communities in Luzhou City in January 2020. The subjects in this clinical trial were recruited from the 401 older adults who participated in the survey. The inclusion criteria were age ≥60 years, diagnosed with sarcopenia according to the Asian Working Group for Sarcopenia 2019 criteria (2). The exclusion criteria were bone and joint diseases of the spine and limbs (such as rheumatoid arthritis), chronic cardiac insufficiency (heart failure or inability to act normally), advanced tumor, implanted pacemaker, clinically visible edema, liver and kidney failure, and cognitive impair. We provided informed consent to participants who met the inclusion and exclusion criteria, and 34 participants who signed the informed consent were enrolled as study subjects, then, we conducted baseline assessment among the 34 subjects. This study was performed in accordance with the Declaration of Helsinki's ethical principles for medical research involving human subjects and approved by the Research Ethics Committee of the Affiliated Hospital of Southwest Medical University (approval no.: KY2019176). The trial protocol was registered at http://www.chictr.org.cn/showproj.aspx?proj=47571 as ChiCTR2000028778.

Sample size

To confirm the hypothesis that HMB supplementation can significantly improve muscle mass, strength, and physical performance, we analyzed the differences in muscle mass, strength, and physical performance between the HMB group (HMBG) and placebo group(PG) . Therefore, we estimated that a sample size of 28 subjects (14 subjects per group) was needed to detect a moderate effect size (Cohen's f = 0.25) (22) for the significant effect of HMB at 3-repeated measurements, with alpha=0.05, power=0.8 (two-sided). Considering an estimated 20% drop-out and non-compliance, at least 34 subjects were needed, which was exactly met by our final sample size. The calculation was performed on G*Power 3.1 (Heinrich-HeineUniversität Düsseldorf).

Randomization and masking

One researcher (Tingting Li) prepared the randomization scheme, used SAS 9.1 software to generate random number, and assigned the subjects to HMBG or PG. The allocation key and security code were stored by Tingting Li. Random numbers containing 1 and 2 were generated according to SAS 9.1 software. Subjects were numbered in chronological order and then correlated one-to-one with the generated random numbers. The corresponding numbers were assigned as 1 to the HMBG and 2 to the PG. The allocation key and specific grouping were masked from the subjects, the dispenser of HMB or placebo, exercise trainers, measurers of outcomes, and analysts to conceal the allocation. The SAS code of randomization is listed in the Appendix Figure 1.

HMB and placebo supplementation

All subjects were previously informed about the intervention protocol, including HMB dosage, time for intake and frequency before the randomization. During the whole intervention period, the HMBG and PG were respectively instructed to consume HMB products and placebos (both produced by NOURIGEN America). The placebo contained the same ingredients as the HMB products except for HMB and had the same appearance and flavor as the HMB products. One sachet (3 g) of the HMB product contained 1.5 g of Ca HMB, 20 kJ of energy, 0 g of protein, 0 g of fat, 1.2 g of carbohydrates, and 15 mg of sodium. One independent researcher (Tingting Li) labeled the packages with the identification code and name of each subject and sent them to the dispensers who were masked from the allocation key (Xinyu Chen and Junliang Zhou), who then distributed the packages to the subjects. The subjects were asked to consume two sachets daily with 50–200mL warm boiled water, in the morning and evening. Individual compliance with HMB or placebo supplementation was monitored by asking subjects to return the empty sachets.

RET

Both the HMBG and PG received the supervised RET. The training program involved elastic belt resistance exercise using a Thera-Band (Yellow, 3 lbs when stretched to twice its length) according to the American College of Sports Medicine's guideline for exercise prescription (23), modified and improved by a doctor (Wei Jiang) from the Department of Rehabilitation, Affiliated Hospital of Southwest Medical University. The training program consisted of the following: warm-up (5 min), stretching; elastic belt resistance exercise (30 min) including nine movements (elbow flexion, side lift, sitting chest, sitting rowing, hip flexion, hip abduction, hip back extension, sitting position lift knee, standing posture lift heel); relaxed walking

(5 min), stretching. The training was performed twice a week, and the nine movements were performed as two sets of five to eight repetitions gradually with a 30-second rest between each set. The training program was carried out in a training hall, one researcher (Xinyu Chen) led the exercise and another (Junliang Zhou) verified the proper exercise posture and fitness of the subjects.

Outcome measures

The handgrip strength (HGS), gait speed, five-time chair stand test, body compositions, and anthropometric measurements were measured at baseline, and at 8- and 12-week follow-up visits. Blood samples were collected at baseline and at 12 weeks.

Primary outcome

HGS has been reported as an important predictor of quality of life and is related to adverse outcomes in the elderly (24, 25); this study therefore selected the change in HGS from baseline to 8 and 12 weeks as the primary outcome. Handgrip strength (Kg) was measured on the dominant hand using a Jamar Plus+ Dynamometer. During the measurement, each subject was in an upright position, with the feet naturally separated and arms naturally dropped. The subjects was then asked to squeeze the handgrip instrument with the dominant hand with maximum effort maintaining the contraction for approximately 5 s (26). Three measurements of handgrip strength were recorded separately, and the maximum value of the measurements was used for analysis.

Secondary outcomes

Gait speed (m/s) was evaluated based on the time required to complete a walk of 6 m at each subject's usual pace (2). The uniformly trained investigators used a stopwatch to record the time, the measurement was taken twice per subject and the average of the two walking times was used. The five-time chair stand test (s) assessed the time required from getting up from a chair to sitting back down five consecutive times without any aid, including armrests; the subjects were instructed to cross their arms on their chest, stand up, and sit back down (27).

Anthropometric measurements including weight (kg) and height (m) were measured using an electronic scale. Body compositions such as skeletal muscle mass (SMM), soft lean mass (SLM), fat-free mass (FFM), and FFM of the right arm were measured using a bioelectrical impedance analysis (BIA) device (InBody 770 device, Bioimpedance, Seoul, Korea). The skeletal muscle index (SMI) was calculated as SMM/height^2. Muscle quality (MQ) was calculated as HGS/FFM of the right arm (28).

The blood samples were collected from the antecubital vein of the subjects when fasting. The recorded blood parameters included the following: inflammatory factors containing tumor necrosis factor-like weak inducer of apoptosis (TWEAK) and interleukin-18 (IL-18); glycolipid metabolism indexes including fasting blood-glucose, total cholesterol, triglyceride, low-density lipoprotein cholesterol (LDL cholesterol), high-density lipoprotein cholesterol (HDL cholesterol); indexes of liver and kidney function including alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), direct bilirubin (DBIL), indirect bilirubin (IDBIL), total bile acid (TBA), blood urea nitrogen (BUN), uric acid (UN), creatinine (CREA), and glomerular filtration rate (GFR). All blood tests were performed at the Department of Clinical Laboratory, The Affiliated Hospital of Southwest Medical University, Luzhou City, Sichuan Province, China. There were no non-detect within the blood samples, indexes for all samples had specific test results in our study.

Statistical analyses

The baseline characteristics were presented as mean ± standard deviation for continuous variables, and counts(percentage) for categorical variables. The t-tests or Mann-Whitney U test for continuous data, χ^2 tests for categorical data were used to evaluate group differences at baseline. The missing data caused by the dropping-out were imputed by the last observation carried forward (29). Analysis of covariance(ANCOVA) was performed to analyze the main effect of HMB at 8 and 12 weeks, mean changes at 8 and 12 weeks from baseline were defined as dependent variable and tested between groups, group was defined as fixed factors, baseline level and baseline SMM were defined as covariates. Statistical analyses were performed using SPSS v25.0 (SPSS Statistics; IBM, Armonk, NY) All statistical tests were two-tailed, with significance set at $P < 0.05$.

Results

Subjects and Baseline characteristics

Of the 401 survey participants, 106 were diagnosed with sarcopenia; 72 refused to participate because of remote residence, inconvenient transportation, refusal of venous blood collection, and private time schedule conflict with trial. Ultimately, 34 subjects agreed to participate in this trial. Baseline characteristics of the HMBG and PG are presented in Table 1.

Follow-up and Safety

At 8 weeks, one subject in the HMBG dropped out because private time schedule conflict with trial. At 12 weeks, one subject in the HMBG dropped out because of a change in residence; while three subjects in the PG dropped out because of the following reasons: one for changing residence, one for travel, and one for refusal of repeated venous blood collection (Figure 1). The discrepancies in the baseline characteristics among the subjects who completed the study and dropped out were not significant, except for age and the five-time chair stand test (Appendix Table 1). The indexes of liver and

kidney functions showed no significant difference between the HMBG and PG at baseline and 12 weeks except for AST (Appendix Table 2). The difference of proportions of subjects who had liver and kidney function indexes in normal range at baseline and in abnormal range at 12 weeks between the HMBG (8(44.40%)) and the PG (5(31.30%)) had no statistical significance (χ^2=0.624, P=0.429). The abnormal indexes were GFR (3 subjects), TBA (2 subjects), both TBA and UN (1 subject), both BUN and UN (1 subject), ALT (1 subject) in the HMBG; GFR (4 subjects), both GFR and TBA (1 subject) in the PG. No adverse events were reported during the intervention period.

Table 1. Baseline characteristics of the subjects in HMBG and PG

Variable	HMBG (n=18) mean ± SD/count (percentage)	PG (n=16) mean ± SD/count (percentage)
Age (years)	72.89±7.02	71.44±5.22
Women (n (%))	11(61.10%)	11(68.80%)
Hand grip strength (kg)	23.16±9.12	21.29±6.58
Gait speed (m/s)	1.07±0.21	1.08±0.19
Five-time chair stand test(s)	17.01±4.35	14.64±2.39
SMM (kg)	19.40±3.70	19.89±3.78
SMI (kg/m^2)	5.78±0.96	5.88±0.85
FFM (kg)	36.47±6.11	37.27±6.25
SLM (kg)	34.32±5.86	35.12±5.98
FFM of the right arm (kg)	1.72±0.50	1.80±0.49
MQ (kg kg−1)	13.35±3.13	11.99±3.17
TWEAK (pmol/mL)	31.41±25.38	35.46±21.90
IL-18 (pgl/mL)	118.66±103.33	102.86±91.42
Fasting blood-glucose (mmol/L)	5.78±1.85	5.68±2.50
Total cholesterol (mmol/L)	4.75±0.83	4.63±1.05
Triglyceride (mmol/L)	1.32±0.61	1.35±0.95
LDL cholesterol (mmol/L)	2.94±0.72	2.79±1.07
HDL cholesterol (mmol/L)	1.39±0.39	1.40±0.31

SD: standard deviation. PG, placebo group; FFM, fat-free mass; HMBG, HMB group; HGS, handgrip strength; HDL cholesterol, high-density lipoprotein cholesterol; IL-18, interleukin-18; LDL cholesterol, low-density lipoprotein cholesterol; MQ, muscle quality (HGS/FFM of the right arm); SMM, skeletal muscle mass; SMI, skeletal muscle mass index; SLM, soft lean mass; TWEAK, tumor necrosis factor-like weak inducer of apoptosis.

Primary outcome

At 12 weeks, the HMBG had significant improvement in HGS, while the PG had a decline in HGS compared to that at baseline. The HMBG had significantly greater improvement than the PG (P <0.001) at 12 weeks (Table 2; Figure 2, a).

Secondary outcomes

The five-time chair stand test significantly improved at 8 and 12 weeks in both groups, while gait speed increased at 12 weeks only in the HMBG. Compared with the PG, the HMBG had statistically greater improvement in five-time chair stand test (P = 0.001) and greater gait speed (P = 0.014) at 12 weeks (Table 2; Figure 2, b,c).

No significant differences in body composition were observed at any time between the groups (Table 2).

The HMBG indicated a significant improvement in MQ at 12 weeks compared to the baseline, and had statistically better improvement in the HMBG compared with the PG at 12 weeks (P = 0.001) (Table 2; Figure 2, d).

The TWEAK and IL-18 significantly decreased in the HMBG at 12 weeks compared to baseline values. The TWEAK improvement in the HMBG was greater than that in the PG at 12 weeks (P = 0.041), while no significant difference in IL-18 was observed between the groups(Table 2 ;Figure 2, e,f).

The glycolipid metabolism indexes including fasting blood-glucose, total cholesterol, triglyceride, LDL cholesterol, HDL cholesterol showed no differences between the groups at 12 weeks (Table 2).

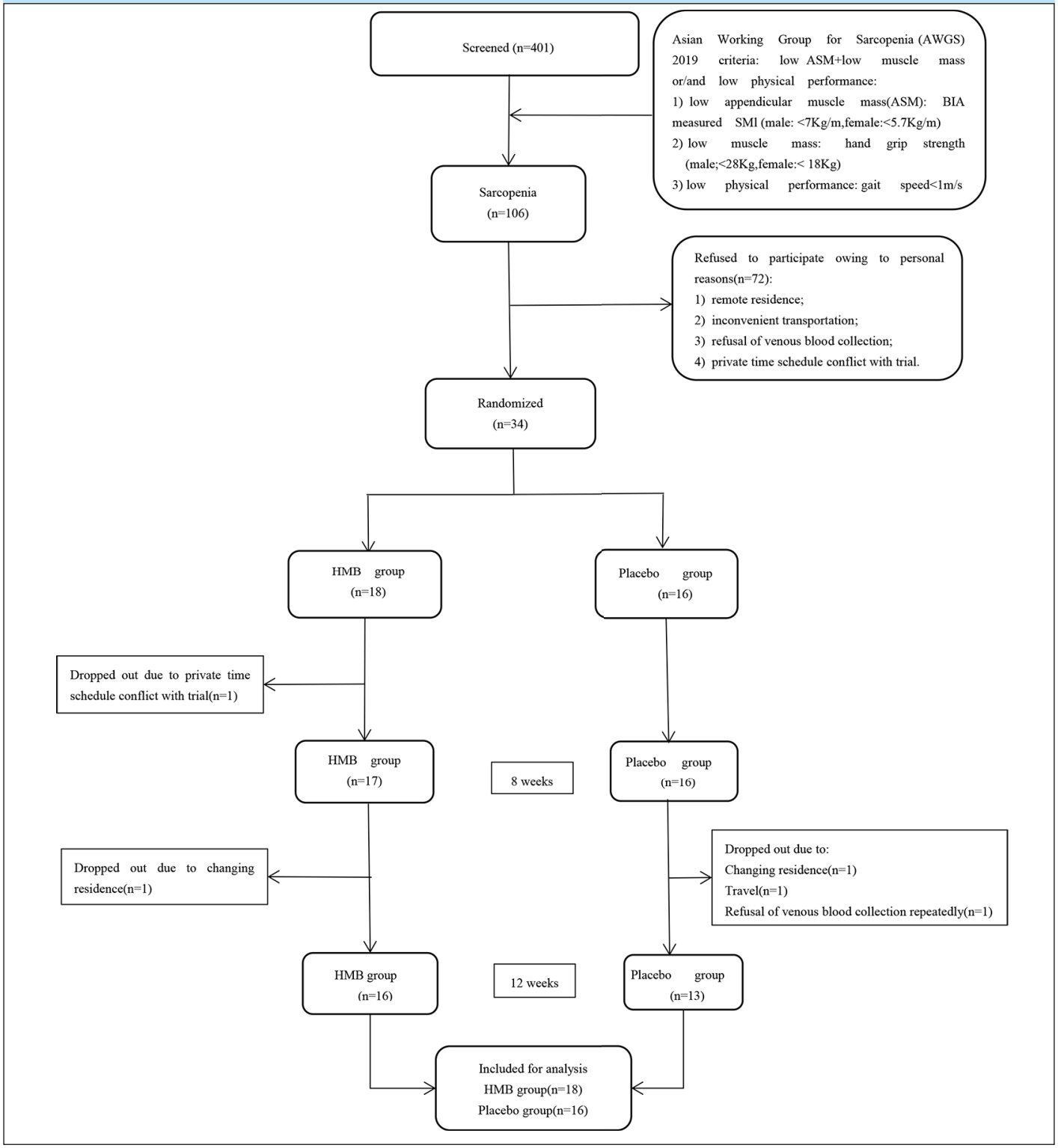
Discussion

Our results demonstrated that HMB significantly improved the effect of resistance exercise training on HGS, gait speed, five-time chair stand test, MQ and TWEAK in older adults with sarcopenia. But no significant differences in SMM, SMI, FFM, and SLM between the HMBG and PG were observed at 12 weeks. There was no impact of HMB on glucose and lipid metabolism indexes.

After the 12-week intervention, the HGS, gait speed and five-time chair stand test in HMBG showed significantly greater improvement compared with the PG; these results were similar to those in Nasimi's study of sarcopenia older adults consuming HMB 3g daily (30). Our results were different to that in Osuka's study of older women with low muscle mass who consumed HMB 1.2g daily (30); in that study, HMB slightly improved gait speed by 0.06m/s, but did not promote HGS and five-time chair stand test. The different HMB dosage may partly contribute to the different results, as shown in Nissen et al's study which indicated a dose-dependent increase in total body strength with three levels of HMB supplementation at 0, 1.5, 3 grams per day (32). Previous studies have demonstrated that hand grip strength is a crucial predictor of adverse outcomes including comorbidity, hospitalization, poor prognosis and mortality, and is significantly related to mobility and quality of life in older adults (24, 25). Our results show that the HGS of the HMBG significantly increased by approximately 2.68 (95%CI:1.29, 4.07) kg after the 12-week intervention, which has crucial clinical value, considering that the likelihood of all-cause mortality is lowered by 13% for every 1 kg increment in HGS over 1 year (33).

Zhu et al indicated that HMB increased lower limb muscle mass in addition to RET in 12 weeks intervention, but the increase was not sustained for 24 weeks without HMB consumption in 12-24 weeks even with continued RET; this is probably because the cessation of HMB supplementation reduced the anabolism of protein (20). In our study, the SMM, SMI, SLM, FFM, and FFM of the right arm had no significant differences between HMBG and PG, which were analogous to Nasimi's study (30). Patients with sarcopenia have mainly

Figure 1. Flow diagram of randomization and intervention



"primary sarcopenia" with characteristic of anabolic resistance (34), so observing a statistical improvement in muscle mass may take longer in such patients. This could be the reason why the between-group differences were not statistically significant at 12 weeks.

The latest definition of sarcopenia of the European Working Group on Sarcopenia in Older People suggests that the loss of muscle strength with aging is faster than that of muscle mass(35), so there could be other factors for strength loss besides muscle mass reduction. MQ, which is calculated as muscle strength per unit of muscle mass can reflects the health state of muscle comprehensively (36), and can be a good approach to estimate the strength production capacity of skeletal muscle tissue (37). A notable finding of our study

Table 2. Changes in primary and secondary outcomes in HMBG and PG over time

	HMBG n=18	PG n=16	Between-group effect size(t/ partial η2)	P value
Primary outcome				
Hand grip strength (kg)				
Baseline (mean±SD)	23.16±9.12	21.29±6.58	0.675	0.505
8 weeks (mean±SD)	23.92±8.78	20.88±5.37		
Change from baseline (mean±SD)	0.76±1.64	-0.41±3.64		
LS means (mean±SE(95%CI))	0.91±0.63 (-0.376, 2.20)	-0.58±0.67 (-1.95, 0.79)		
Differences between groups (mean±SE(95%CI))	1.49±0.94(-0.43, 3.41)		0.077	0.124
12 weeks (mean±SD)	25.77±8.50	19.44±4.43		
Change from baseline (mean±SD)	2.62±2.04	-1.85±3.28		
LS means (mean±SE(95%CI))	2.68±0.55 (1.56, 3.80)	-1.92±0.58 (-3.11,-0.73)		
Differences between groups (mean±SE(95%CI))	4.61±0.82 (2.93; 6.28)		0.513	<0.001
Secondary outcome				
Gait speed (m/s)				
Baseline (mean±SD)	1.07±0.21	1.08±0.19	-0.138	0.891
8 weeks (mean±SD)	1.07±0.13	1.03±0.13		
Change from baseline (mean±SD)	0.00±0.14	-0.05±0.17		
LS means (mean±SE(95%CI))	0.00±0.02 (-0.05, 0.05)	-0.04±0.03 (-0.10, 0.01)		
Differences between groups (mean±SE(95%CI))	0.04±0.04(-0.03,0.11)		0.043	0.257
12 weeks (mean±SD)	1.22 ±0.13	1.11 ±0.13		
Change from baseline (mean±SD)	0.14±0.21	0.02±0.19		
LS means (mean±SE(95%CI))	0.14±0.03 (0.08, 0.20)	0.03±0.03 (-0.03, 0.09)		
Differences between groups (mean±SE(95%CI))	0.11±0.04 (0.02, 0.20)		0.184	0.014
Five-time chair stand test(s)				
Baseline (mean±SD)	17.01±4.35	14.64±2.39	1.964	0.061
8 weeks (mean±SD)	12.88±3.61	12.59±3.04		
Change from baseline (mean±SD)	-4.13±2.68	-2.05±2.91		
LS means(mean±SE (95%CI))	-3.73±0.62 (-4.99, -2.47)	-2.50±0.66 (-3.84,-1.16)		
Differences between groups (mean±SE(95%CI))	-1.23±0.93(-3.12, 0.66)		0.056	0.193
12 weeks (mean±SD)	9.23±3.57	11.86±2.50		
Change from baseline (mean±SD)	-7.78±4.23	-2.79±2.26		
LS means (mean±SE(95%CI))	-7.15±0.68 (-8.52,-5.77)	-3.50±0.72 (-4.96,-2.03)		
Differences between groups (mean±SE(95%CI))	-3.65±1.01(-5.72,-1.58)		0.302	0.001
SMM (kg)				
Baseline (mean±SD)	19.40±3.70	19.89±3.78	-0.384	0.703
8 weeks (mean±SD)	19.70±3.64	20.11±3.70		
Change from baseline (mean±SD)	0.30±0.79	0.22±0.47		
LS means (mean±SE(95%CI))	0.29±0.16 (-0.02, 0.61)	0.23±0.16 (-0.11, 0.56)		
Differences between groups (mean±SE(95%CI))	0.06±0.23 (-0.40, 0.53)		0.003	0.778
12 weeks (mean±SD)	19.60±3.84	19.76±3.28		
Change from baseline (mean±SD)	0.19±3.92	-0.13±3.01		
LS means (mean±SE(95%CI))	0.08±0.73 (-1.40, 1.56)	-0.01±0.77 (-1.57,1.56)		
Differences between groups (mean±SE(95%CI))	0.09±1.06(-2.07,2.25)		0.000	0.935
SMI (kg/m²)				
Baseline (mean±SD)	5.78±0.96	5.88±0.85	-0.313	0.756
8 weeks (mean±SD)	5.88±0.94	5.97±0.80		
Change from baseline (mean±SD)	0.10±0.21	0.09±0.16		
LS means (mean±SE(95%CI))	0.10±0.04 (-0.01, 0.19)	0.09±0.05 (-0.05, 0.19)		
Differences between groups (mean±SE(95%CI))	0.01±0.06 (-0.12, 0.14)		0.000	0.917

Table 2 (Continued). Changes in primary and secondary outcomes in HMBG and PG over time

	HMBG n=18	PG n=16	Between-group effect size(t/ partial η2)	P value
12 weeks (mean±SD)	5.88±0.89	5.85±0.80		
Change from baseline (mean±SD)	0.09±0.97	-0.03±0.71		
LS means (mean±SE(95%CI))	0.06±0.18 (-0.30, 0.42)	0.00±0.19 (-0.38, 0.38)		
Differences between groups (mean±SE(95%CI))	0.06±0.26(-0.46, 0.58)		0.002	0.814
FFM (kg)				
Baseline (mean±SD)	36.47±6.11	37.27±6.25	-0.378	0.708
8 weeks (mean±SD)	37.00±5.97	37.61±6.14		
Change from baseline (mean±SD)	0.53±1.32	0.34±0.89		
LS means (mean±SE(95%CI))	0.51±0.27 (-0.04, 1.07)	0.36±0.29 (-0.23, 0.95)		
Differences between groups (mean±SE(95%CI))	0.15±0.40(-0.66, 0.96)		0.005	0.705
12 weeks (mean±SD)	36.90±6.10	37.43±5.57		
Change from baseline (mean±SD)	0.43±1.43	0.16±1.10		
LS means (mean±SE(95%CI))	0.40±0.29 (-0.19, 1.00)	0.19±0.31(-0.44, 0.82)		
Differences between groups (mean±SE(95%CI))	0.21±0.43(-0.65, 1.08)		0.008	0.619
SLM (kg)				
Baseline (mean±SD)	34.32±5.86	35.12±5.98	-0.395	0.696
8 weeks (mean±SD)	34.82±5.74	35.43±5.84		
Change from baseline (mean±SD)	0.50±1.25	0.31±0.85		
LS means (mean±SE(95%CI))	0.49±0.26 (-0.04, 1.01)	0.33±0.27 (-0.23, 0.88)		
Differences between groups (mean±SE(95%CI))	0.16±0.38 (-0.61 ,0.93)		0.006	0.67
12 weeks (mean±SD)	34.75±5.83	35.24±5.34		
Change from baseline (mean±SD)	0.43±1.35	0.12±1.00		
LS means (mean±SE(95%CI))	0.41±0.27 (-0.15, 0.97)	0.15±0.29 (-0.44, 0.74)		
Differences between groups (mean±SE(95%CI))	0.26±0.40(-0.55, 1.08)		0.014	0.515
FFM of the right arm (kg)				
Baseline (mean±SD)	1.72±0.50	1.80±0.49	-0.500	0.621
8 weeks (mean±SD)	1.75±0.48	1.82±0.50		
Change from baseline (mean±SD)	0.03±0.13	0.02±0.10		
LS means (mean±SE(95%CI))	0.03±0.03 (-0.03, 0.09)	0.02±0.03 (-0.04, 0.08)		
Differences between groups (mean±SE(95%CI))	0.01±0.04(-0.07, 0.10)		0.003	0.751
12 weeks (mean±SD)	1.77±0.49	1.82±0.46		
Change from baseline (mean±SD)	0.06±0.16	0.02±0.07		
LS means (mean±SE(95%CI))	0.05±0.03 (-0.01, 0.11)	0.03±0.03 (-0.03, 0.09)		
Differences between groups (mean±SE(95%CI))	0.02±0.04(-0.06, 0.11)		0.011	0.561
MQ (kg kg−1)				
Baseline (mean±SD)	13.35±3.13	11.99±3.17	1.251	0.220
8 weeks (mean±SD)	13.64±3.13	11.80±2.99		
Change from baseline (mean±SD)	0.30±1.69	-0.20±1.99		
LS means (mean±SE(95%CI))	0.40±0.42 (-0.46, 1.26)	-0.31±0.45 (-1.22, 0.60)		
Differences between groups (mean±SE(95%CI))	0.71±0.62(-0.56, 1.98)		0.041	0.264
12 weeks (mean±SD)	14.66±3.21	11.00±3.03		
Change from baseline (mean±SD)	1.31±2.29	-0.99±1.66		
LS means (mean±SE(95%CI))	1.39±0.44 (0.50, 2.29)	-1.08±0.47 (-2.03, -0.13)		
Differences between groups (mean±SE(95%CI))	2.47±0.65(1.15, 3.80)		0.327	0.001
TWEAK (pmol/mL)				
Baseline (mean±SD)	31.41±25.38	35.46±21.90	-0.495	0.624
12 weeks (mean±SD)	16.93±5.96	34.75±31.95		
Change from baseline (mean±SD)	-14.48±26.81	-0.71±43.40		
LS means (mean±SE(95%CI))	-15.16±4.84 (-25.06,-5.27)	0.06±5.14 (-10.44, 10.57)		

Table 2 (Continued). Changes in primary and secondary outcomes in HMBG and PG over time

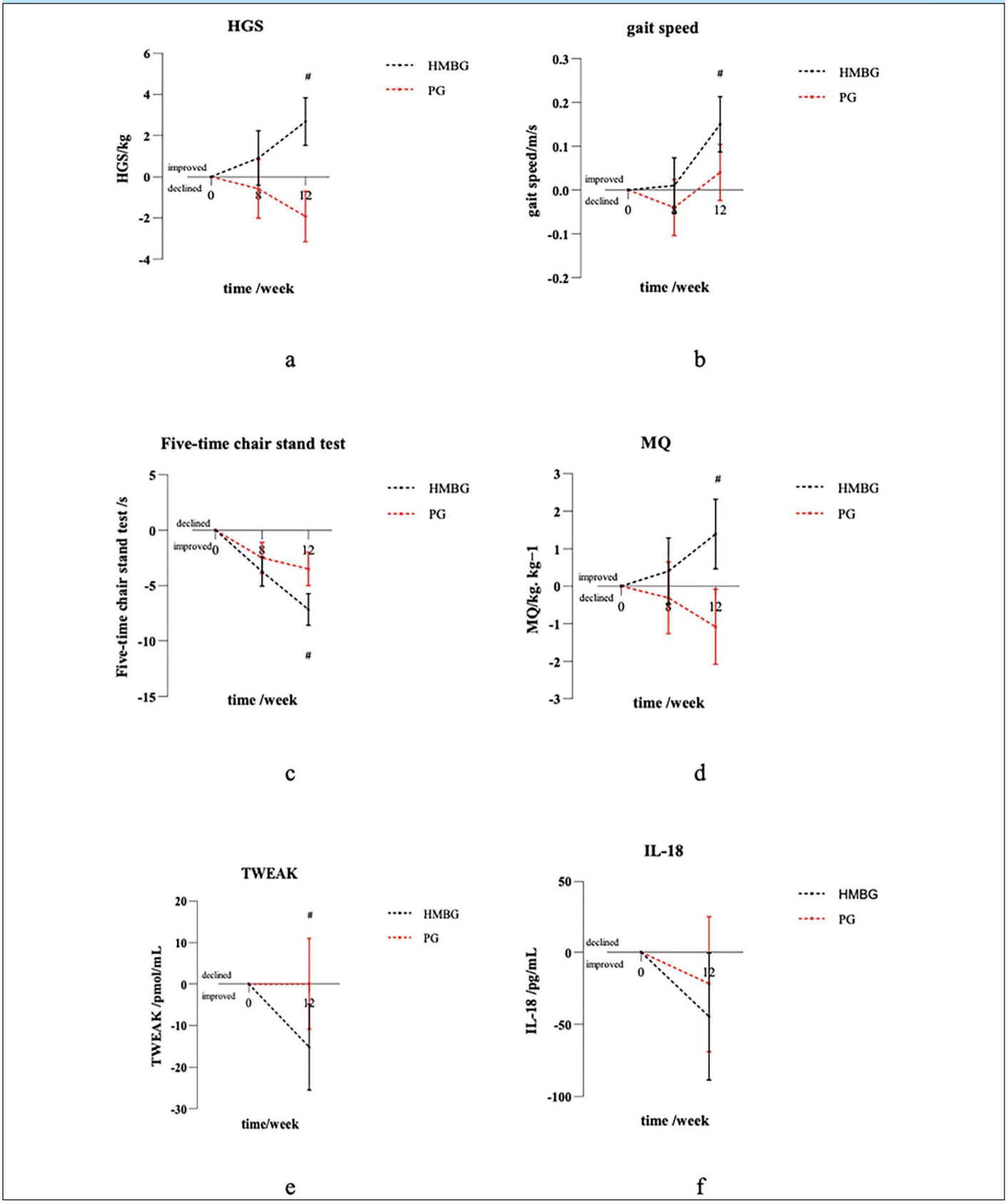
	HMBG n=18	PG n=16	Between-group effect size(t/ partial η2)	P value
Differences between groups (mean±SE(95%CI))	-15.23±7.13(-29.80, -0.66)		0.132	0.041
IL-18 (pgl/mL)				
Baseline (mean±SD)	118.66±103.33	102.86±91.42	0.469	0.642
12 weeks (mean±SD)	71.84±80.54	85.50±137.02		
Change from baseline (mean±SD)	-46.82±99.21	-17.36±92.89		
LS means (mean±SE(95%CI))	-42.92±20.88 (-85.55, -0.28)	-21.75±22.15 (-66.98, 23.48)		
Differences between groups (mean±SE(95%CI))	-21.17±30.51(-83.47, 41.14)		0.016	0.493
Fasting blood-glucose(mmol/L)				
Baseline (mean±SD)	5.78±1.85	5.68±2.50	0.128	0.899
12 weeks (mean±SD)	7.34±3.07	7.19±2.85		
Change from baseline (mean±SD)	1.56±2.97	1.51±3.28		
LS means (mean±SE(95%CI))	1.62±0.68 (0.23, 3.02)	1.44±0.73 (-0.04, 2.92)		
Differences between groups (mean±SE(95%CI))	0.19±1.00 (-1.86, 2.23)		0.001	0.854
Total cholesterol (mmol/L)				
Baseline (mean±SD)	4.75±0.83	4.63±1.05	0.389	0.700
12 weeks (mean±SD)	5.10±0.86	4.84±0.94		
Change from baseline (mean±SD)	0.35±0.71	0.22±0.44		
LS means (mean±SE(95%CI))	0.37±0.13 (0.09, 0.64)	0.19±0.14 (-0.10, 0.49)		
Differences between groups (mean±SE(95%CI))	0.17±0.20 (-0.23, 0.57)		0.025	0.387
Triglyceride (mmol/L)				
Baseline (mean±SD)	1.32±0.61	1.35±0.95	-0.116	0.908
12 weeks (mean±SD)	1.32±0.61	1.29±0.65		
Change from baseline (mean±SD)	0.00±0.49	-0.06±0.84		
LS means (mean±SE(95%CI))	-0.00±0.13 (-0.26, 0.26)	-0.05±0.13 (-0.33, 0.22)		
Differences between groups (mean±SE(95%CI))	0.05±0.19 (-0.33, 0.43)		0.003	0.778
LDL cholesterol (mmol/L)				
Baseline (mean±SD)	2.94±0.72	2.79±1.07	0.476	0.637
12 weeks (mean±SD)	3.24±0.79	2.93±0.89		
Change from baseline (mean±SD)	0.30±0.50	0.14±0.58		
LS means (mean±SE(95%CI))	0.33±0.12 (0.09, 0.57)	0.11±0.12 (-0.14, 0.37)		
Differences between groups (mean±SE(95%CI))	0.21±0.17 (-0.14, 0.56)		0.049	0.223
HDL cholesterol (mmol/L)				
Baseline (mean±SD)	1.39±0.39	1.40±0.31	-0.128	0.899
12 weeks (mean±SD)	1.47±0.41	1.50±0.34		
Change from baseline (mean±SD)	0.08±0.15	0.10±0.29		
LS means (mean±SE(95%CI))	0.08±0.05 (-0.03, 0.18)	0.11±0.06 (0.00, 0.22)		
Differences between groups (mean±SE(95%CI))	-0.03±0.08 (-0.18, 0.12)		0.005	0.689

SD, standard deviation; SE, standard error; 95%CI, 95% confidence interval. PG, placebo group; FFM, fat-free mass; HMBG, HMB group; HGS, handgrip strength; HDL cholesterol, high-density lipoprotein cholesterol; IL-18, interleukin-18; LDL cholesterol, low-density lipoprotein cholesterol; MQ, muscle quality (HGS/FFM of the right arm); SMM, skeletal muscle mass; SMI, skeletal muscle mass index; SLM, soft lean mass; TWEAK, tumor necrosis factor-like weak inducer of apoptosis. Change from baseline was the differences between the 8weeks or 12weeks and baseline. LS means were the least-squares means of the change from baseline. Difference between groups was the difference of LS means between groups. The between-group effect size was t or partial η2 for comparison of baseline variables or LS means between HMBG and PG.

is that MQ in the HMBG had a greater increase than that in the PG; this is consistent with Stout et al.'s results where MQ significantly increased only in the HMB intervention group (4).

We observed significant improvement in TWEAK and IL-18 in the HMBG compared to baseline values, and a greater improvement of TWEAK in the HMBG compared with the PG at 12 weeks; this has not been reported in previous studies. According to one previous study, the serum TWEAK level is significantly associated with sarcopenia, and can predict the severity of sarcopenia (38). TWEAK can reduce mitochondrial content and oxidative phosphorylation, inhibit angiogenesis of muscle, leading to the development of sarcopenia (39). We observed no impact of HMB on fasting blood-glucose, which did not validate literature reports that HMB impairs peripheral insulin sensitivity (40).

Figure 2. The differences (mean and 95%CI) of HGS, gait speed, five-time chair stand test, MQ, TWEAK and IL-18 between 8 or 12 weeks with baseline in both groups. PG, placebo group; HMBG, HMB group; HGS, handgrip strength; IL-18, interleukin-18; MQ, muscle quality (HGS/FFM of the right arm); TWEAK, tumor necrosis factor-like weak inducer of apoptosis



#Significant between-group effect (P<0.05).

The strengths of our study are as follows. Firstly, our results were obtained in sarcopenic older adults, as few studies have specially focused on the effect of HMB on this population; secondly, the HMB product contained HMB without protein, amino acid or other nutrients which have anabolic effects on muscle, so that we were able to directly analyze the independent effects of HMB; also, we observed the additive effect of HMB on sarcopenia based on RET. Nevertheless, our study had some limitations. First, we measured body composition using the BIA device rather than gold standard instruments such as computed tomography or magnetic resonance imaging. Second, we did not measure protein synthesis indicators to estimate the improvement of anabolic resistance. Then, the missing data were imputed by the last observation carried forward, which could bias the results, but it still can provide good estimation when the proportion of missing data was few and the longitudinal data were carried across within one year (29). Finally, the sample size was small, which may have resulted in a lack of statistical significance for some parameters.

In conclusion, HMB supplementation can enhance the effect of resistance exercise training on muscle strength, physical performance and MQ in older adults with sarcopenia. Therefore, HMB supplementation could be an effective treatment for sarcorpenia. Additional large sample size and multi-center studies are needed to confirm the effects of HMB supplementation on sarcopenia in older adults.

Conflict of Interest: The research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions: Chan Yang and Yu Song performed the statistical analysis, drafted the manuscript. Tingting Li conceived the idea, designed and conducted the trial, managed the project and subjects. Hong Jia supervised the study and review the manuscript. Xinyu Chen and Junliang Zhou performed the investigation, intervention and data collection. Qing Pan: performed the statistical analysis; Wei Jiang and Min Wang: instructed the intervention. All authors contributed to the article and approved the submitted version.

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