Supplementary Data For: An umbrella review of systematic reviews of β-hydroxy-β-methyl butyrate (HMB) supplementation in promoting skeletal muscle mass and function in aging and clinical practice

Supplementary table 1 - Standardized Effectiveness Statements, from [1]

| Summary statement | Translation |
|-------------------|-------------|
| **Sufficient evidence** | Evidence to make a decision about the effect of the intervention(s) in relation to a specific outcome(s). This includes evidence of an effect in terms of (i) benefit or (ii) harm. Statistically significant results are considered to represent sufficient evidence on which to base decisions, but a judgement of sufficient evidence is also made based on the number of studies/participants included in the analysis for a particular outcome. A rating of sufficient evidence is often based on meta-analysis producing a statistically significant pooled result that is based on numerous included studies/participants. This judgement may also be made based on the number of studies and/or study participants showing a statistically significant result - for example a result where 12 studies of a total of 14 for a specific outcome showed a statistically significant effect of an intervention would be considered to represent sufficient evidence. |
| **Some evidence** | Less conclusive evidence to decide about the effects of a particular intervention(s) in relation to a specific outcome(s). In this case, the result is qualified according to the findings of the review - for example, 'some evidence (5 studies of 9) reported a positive effect of .....' (This would be based on a more equivocal set of results than those obtained for 'sufficient evidence' above. For example, while 12/14 statistically significant studies would be classed as 'sufficient evidence', 5/9 statistically significant studies is more equivocal and would be classed as 'some evidence.') This may also be based on a statistically significant result obtained in a small number of studies; a statistically significant result obtained from studies with a small number of participants; or a statistically significant result obtained from studies of low quality; the result is some evidence. |
| **Insufficient evidence** | Not enough evidence to support decisions about the effects of the intervention(s) based on the included studies. This should be interpreted as 'no evidence of effect', rather than 'evidence of no effect'. Statistically non-significant results are considered to represent insufficient evidence. Where the number of studies is small, and/or the number of participants included in the studies is small, insufficient evidence might reflect underpowering of the included studies to be able to detect an effect of the intervention. Where the number of studies is large, and/or the number of participants included in these studies is large, 'insufficient evidence' may reflect underlying ineffectiveness of the intervention to affect the outcomes being examined. In such cases the intervention may additionally be described as 'generally ineffective' in order to separate such results from those cases where insufficient evidence is used to describe results, but this is based on a small number of studies and/or participants (where non-significant results may reflect underpowering of studies rather than ineffectiveness); the result is insufficient evidence. |
| **Insufficient evidence to determine** | Not enough evidence to be able to determine whether an intervention is effective or not based on the included studies. This statement is about reporting gaps in the evidence (i.e., where there are too few studies to be able to determine effects), rather than the situation of the summary statement above, which is about ineffectiveness (e.g. several studies reporting a statistically non-significant result). It is likely to arise when the numbers of included studies are very small; the result is insufficient evidence to determine. |
Supplementary table 2 - Method to rate the quality of the evidence (QoE) supporting each bottom-line statement. From [1]

| Initial Quality of Body of Evidence | AMSTAR |
|-------------------------------------|--------|
| High (4) if systematic review & meta-analysis | -1 if review of moderate quality (AMSTAR: 4–7) |
| Moderate (3) if systematic review (no meta-analysis) | -2 if review of low quality (AMSTAR: 0–3) |

(1 - very low; 2 - low; 3 - moderate; 4 - high)
**Search strategies**

Web of Science core collection:

(((TS=(HMB)) OR TS=(beta-hydroxy-beta-methylbutyrate)) OR TS=(beta-hydroxy-beta-methylbutyrate)) OR TS=(b-hydroxy-b-methylbutyrate)) OR TS=(3-hydroxy-3-methylbutyrate)) AND (TS=systematic review)

63 results

Pubmed:

Search: (((((HMB) OR (beta-hydroxy-beta-methylbutyrate)) OR ((3-hydroxy-3-methylbutyrate))) ) ) AND (systematic review)

Sort by: Most Recent

"HMB"[All Fields] OR "beta hydroxyisovaleric acid"[Supplementary Concept] OR "beta hydroxyisovaleric acid"[All Fields] OR "beta hydroxy beta methylbutyrate"[All Fields] OR "3-hydroxy-3-methylbutyrate"[All Fields]) AND ("systematic review"[Publication Type] OR "systematic reviews as topic"[MeSH Terms] OR "systematic review"[All Fields])

76 results

Embase:

Database: Embase <1974 to 2021 August 25>

Search Strategy:

1. ((HMB or beta-hydroxy-beta-methylbutyrate or 3-hydroxy-3-methylbutyrate or b-hydroxy-b-methylbutyrate or beta hydroxy beta methylbutyrate or beta-hydroxy beta-methylbutyrate or beta-hydroxy beta methylbutyrate or beta hydroxy beta methylbutyrate) and (systematic review or systematic)).af. (159)

2. Heavy menstrual bleeding.af. (2014)

3. 1 not 2 (90)

90 results
### Supplementary Table 3 - Systematic reviews, including details, included in the analysis

| Reference   | No. of articles (no. of participants) | MA | Results/findings$^a$ | Standardized effectiveness statement | AMSTAR | Bottom-line statement about the main effects of interventions and recommendation within each intervention category | QoE | Declares Conflicts of interest |
|-------------|---------------------------------------|----|----------------------|--------------------------------------|--------|-------------------------------------------------------------------------------------------------|-----|-----------------------------|
| Bear 2019 [2] | 13 (1635)                              | Y  | Body weight: “No effect on bodyweight” (SMD = 0.16; 95% CI: -0.08, 0.41; z = 1.34; P = 0.18; I² = 67%; P = 0.0003) | Some evidence in favour of no difference | 9      | “HMB, and supplements containing HMB, increased muscle mass and strength in a variety of clinical conditions, although the effect size was small.” | 4   | Yes                         |
|             |                                       | Y  | Skeletal muscle mass: “some evidence to support the effect of HMB alone, or supplements containing HMB, on increasing skeletal muscle mass” (SMD = 0.25; 95% CI: -0.00, 0.50; z = 1.93; P = 0.05; I² = 58%; P = 0.01) | Some evidence in favour of no difference |        |                                                                                                |     |                             |
|             |                                       | Y  | Fat mass: “no evidence to support a change in fat mass between patients receiving HMB and controls” (SMD = 0.03; 95% CI: -0.27, 0.34; z = 0.21; P = 0.83; I² = 58%; P = 0.03) | Some evidence in favour of no difference |        |                                                                                                |     |                             |
|             |                                       | Y  | Muscle strength: “Six studies were included in the meta-analysis, revealing strong evidence that HMB or supplements containing HMB improved muscle strength compared with controls, but with | Some evidence in favour of intervention |        |                                                                                                |     |                             |
| Beaudart 2017 [3] | 3 (103) | N | Physical function: “0/4 studies reported between-group differences in any outcome of physical function. 2/4 studies reported no significant changes in physical function in the HMB group”. 2/4 studies “reported within-group improvements in physical function over time in the HMB group” | Some evidence in favour of no difference | 5 | “Physical exercise has a beneficial impact on muscle mass, muscle strength, or physical performance in healthy subjects aged 60 years and older. However, the additional effect of dietary supplementation has only been reported in a limited number of studies.” | 2 | Yes |
|---|---|---|---|---|---|---|---|---|---|
| 4 (495) | N | Physical function: “Muscle strength increased with exercises in 2/3 RCTs with no additional effect of HMB” | | | | | | | |
| | | | Muscle mass: “muscle mass increased with exercise in 3/3 RCTs and an interactive effect of HMB was found in 1/3 RCTs” | | | | | | | |
| | | | Fat-free mass: 0/2 studies showed HMB + exercise significantly improving fat-free mass compared to exercising placebo | | | | | | | |
| | | | Lean mass: 1/1 study “showed a significantly greater effect of exercise + Ca-HMB in preventing | | | | | | |
| Beaudart 2018 [4] | 2 (61) | Y | Muscle mass: “results of meta-analyse reported that CaHMB supplementation was only significantly effective on leg lean mass (MD = 0.27; 95% CI: 0.01, 0.54) but not on total lean body mass (MD = 0.95, 95% CI: -0.58; 2.47).” | Insufficient evidence to determine | 5 | “A limited effect of nutritional supplementation on LSTM, muscle power and physical function. Inconsistent positive effects were observed for some specific supplementations (i.e., creatine, EAA or HMB).” | 3 | No |
| 2 (61) | N | Muscle strength — 1/2 only 1 RCT showed improvement in Muscle strength. “In the first study, no effects of HMB on grip strength were found. However, HMB supplementation increased the leg extension peak torque at 60°, significantly different from the placebo group. In the second study, no difference the HMB supplemented group and the placebo group in regards of muscle strength was found.” | Insufficient evidence to determine | | | 2 | |
| Study                | Design | N   | Physical function: 0/2 – neither of the studies showed improvement in physical function. “One of the two studies showed an improvement in the Get Up and Go test for the HMB group without any significant differences between groups, while the other showed no significant declines in physical performance (Get Up and Go test, SPPB test and 5-item physical performance test) in both groups over the bed-rest period.” | Insufficient evidence to determine | Cost (group) | 6* (350) | Insufficient evidence to determine |
|----------------------|--------|-----|---------------------------------------------------------------------------------|----------------------------------|-------------|---------|----------------------------------|
| Costa Riela 2021 [5] | N      |     | Body composition: 5/6 studies showed favorable changes in body composition       | Some evidence in favour of intervention | 1           | No      | “Our study shows that HMB supplementation improves strength and muscle function in elderly. However, there are few clinical trials using HMB supplementation; thus, only 6 articles were used for this analysis. In addition, due to different methodologies, the assessment of HMB actual effectiveness in attenuating the aging process is rather limited.” |
| Muscle Quality: | 1/2 studies showed improvement in muscle quality |
| Muscle Catabolism: | 1/1 studies showed “acute muscle catabolism reduction during the supplementation phase” |
| Physical performance: | 0/1 “No significant changes between groups during total physical performance” |
| 1/1 studies showed improvement in 6MWT (p < 0.04) |
| Strength: | 2/3 studies showed “improvement of strength parameters in the supplemented group” “Supplementation without resistance exercises improved muscle strength and quality. However, in subjects practicing resistance exercise, supplementation seems to have no additional effect” |
| Insufficient evidence to determine |
| Insufficient evidence to determine |
| Insufficient evidence to determine |
| Some evidence in favour of intervention |
| Study                  | Effect | Y/N | Description                                                                 | Evidence | Notes                                                                 |
|------------------------|--------|-----|------------------------------------------------------------------------------|----------|-----------------------------------------------------------------------|
| Courel-Ibáñez 2019 [6] |        | Y   | **Handgrip strength**: “close to showing statistical significance but with a small effect size” (ES = 0.19; 95% CI: -0.03, 0.40; P = 0.067; I² = 0%) |          | “HMB supplementation in addition to physical exercise has no or fairly low impact in improving body composition, muscle strength, or physical performance in adults aged 50 to 80 years compared to exercise alone.” |
|                        |        | Y   | **Leg strength**: NS, (ES = -0.78; 95% CI: -3.16, 1.59; P = 0.291; I² = 91.6%) |          |                                                                       |
|                        |        | Y   | **Muscle mass**: “Almost no effect” (ES = 0.07; 95% CI: -0.69, 0.82; P = 0.833; I² = 90.6%) |          |                                                                       |
|                        |        | Y   | **Fat mass**: “A positive non-significant effect” (ES = 0.61; 95% CI: -0.73, 1.96; P = 0.293, I² = 84.1%) |          |                                                                       |
|                        |        | Y   | **Muscle and strength together**: “HMB did not have any effect” (ES = -0.06; 95% CI: -0.82, 0.71; P = 0.853; I² = 85.8%) |          |                                                                       |
| Cruz-Jentoft 2014 [7]  |        | N   | **Muscle mass loss prevention**: “prevented muscle mass loss in 1/4 studies” |          | “Overall, HMB showed some effects on muscle mass and function in these high-quality” |
| Study                          | Sample Size | Y/N | Findings                                                                                                                                                                                                 | Weight |
|-------------------------------|-------------|-----|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|
| Lin 2021 [8]                  | 7* (417)    | Y   | Muscle strength: “improved muscle strength in 1/4 studies” Physical performance: “improved physical performance in 1/4 studies” Some evidence in favour of no difference 7 | 3      |
| 8* (448)                      | Y           |     | Fat mass: “the pooled result of FM derived from 8 of the 9 included studies in meta-analysis suggests that almost no effect was found in fat mass.” (ES = -0.04; 95% CI: -0.26, 0.18; z = 0.36, P = 0.716, Fixed-effect model; I² = 0%; P = 0.50) Some evidence in favour of no difference 7 |        |
| Martin-Cantero 2021 [9]      | 3 (77)      | Y   | Muscle mass: HMB “showed a significant positive effect on muscle mass measures” (SMD = Some evidence in 7 | 3      |
| Study                        | N | Physical function | Strength | Fat-free mass | Protein synthesis | Evidence | Recommendation |
|------------------------------|---|-------------------|----------|---------------|------------------|----------|----------------|
| Martinez-Rodriguez 2020 [10]| 1 (27) | 1/1 study shows “supplementation with HMB, arginine, and lysine can improve functionality” | Insufficient evidence to determine | Insufficient evidence to determine | Insufficient evidence to determine | 4 | “In older women, supplementation with bicarbonate, HMB, lysine, and arginine also have shown positive effects on exercise performance. Health professionals should be aware of these strategies and consider their use for different interventions or supplementation protocols. No additional or exclusive effects were found in the population of older men.” |

Martinez-Rodriguez 2020 [10]:

0.522; 95%CI: 0.175, 0.868; \( P = 0.003; I^2 = 5.40\%\)

In favour of intervention

supplementation in community-dwelling and institutionalized older adults."

“The HMB supplements used in the studies in the present review mainly consisted of HMB (or calcium HMB) in combination with the essential amino acids arginine and lysine, suggesting that perhaps this combination could be optimal for building and maintaining muscle mass.”

Physical function: 1/1 study shows “supplementation with HMB, arginine, and lysine can improve functionality”

Strength: 1/1 study shows “supplementation with HMB, arginine, and lysine can improve strength”

Fat-free mass: 1/1 study shows “supplementation with HMB, arginine, and lysine can improve fat-free mass”

Protein synthesis: 1/1 study shows “supplementation with HMB, arginine, and lysine can improve protein synthesis”

Insufficient evidence to determine

Insufficient evidence to determine

Insufficient evidence to determine

Insufficient evidence to determine

No additional or exclusive effects were found in the population of older men.”
| Study                  | N | Body Mass | Evidence                      | Grade | Recommendation |
|------------------------|---|-----------|-------------------------------|-------|-----------------|
| Mochamat 2017 [11]     | 2 (504) | Lean body mass: 1/2 studies showed “an increase in lean body mass” | Insufficient evidence to determine       | 6     | “Following the GRADE methodology, no positive recommendation could be expressed for the use of minerals, vitamins, proteins, or other supplements in cancer patients. Further research is needed to identify the efficacy and safety of these supplements to be able to give clear evidence-based recommendations.” | 2     | No |
| Molfino 2013 [12]      | 15 (1176) | Body mass: 2/11 studies found significant improvements in body mass  
Fat-free mass: 4/10 studies found significant improvements in fat-free mass | Some evidence in favour of no difference  
Some evidence in favour of no difference | 1     | “HMB supplementation contributed to preserve FFM in cancer, AIDS, elderly, and following trauma. It also improved contractile performance as well as endurance aerobic performance and muscle strength. It also reduced” | 1     | No |
| Study                        | Lean body mass: | Fat mass: | Muscle strength: | Muscle mass: | Muscle strength and function: | 
|------------------------------|-----------------|-----------|------------------|--------------|-----------------------------| 
| Oktaviana 2019 [13]         | 1/1 studies     | 1/8 studies | 2/5 studies     | 2/2 studies  | 2/2 studies                  |

Lean body mass: 1/1 studies showed “a significant increase of lean body mass in the intervention group compared to control group”

Fat mass: 1/8 studies found significant decreases in fat mass

Muscle strength: 2/5 studies found significant improvements in muscle strength

Muscle mass: 2/2 studies found the intervention group experienced a reduced loss of muscle mass during 10 days of bed rest (one study) or in sarcopenic patients with hip fracture (one study).

Muscle strength and function: 2/2 studies showed “reduced loss of strength and function compared to the control group”

Some evidence in favour of no difference

Insufficient evidence to determine

Insufficient evidence to determine

Insufficient evidence to determine

Insufficient evidence to determine

Exercise-induced markers of muscle damage, post-exercise recovery time and improved quality of life and respiratory function in COPD... Further, well designed clinical studies are needed to confirm effectiveness and mode of action of HMB.”

“This systematic review shows that HMB can improve lean body mass and preserve muscle strength and function in older people with sarcopenia and frailty. Further well-designed RCTs in this area of research are necessary to better identify the role of HMB in this population.”
| Study | N | Description |
|-------|---|-------------|
| Prado 2022 [14] | 15 (943) | N | Insufficient evidence to determine |

**Muscle mass:** 3/4 RCTs found a beneficial effect of HMB supplementation on muscle mass, compared to the control group.

5/8 (4 non-randomized studies of interventions (NRSIs) and 1 RCT) found a beneficial effect of HMB supplementation in the experimental group alone.

**Muscle Strength:** 1/1 RCT found patients who received the HMB/Arg/Gln supplement had a smaller decrease in handgrip strength when compared with controls.

3/3 NRSIs reported a beneficial effect of HMB supplementation on increasing muscle strength.

**Physical Function:** 2/2 NRSI found a beneficial effect on 4-mgait speed, however only one was found to be statistically significant.

**Body weight:** 2/4 RCT found a beneficial effect of HMB supplementation.

1/1 NSRI found a *mixed* effect of HMB supplementation.

Some evidence in favour of intervention

This comprehensive systematic review found some evidence of a beneficial effect of HMB supplementation on muscle mass, function, hospitalization outcomes, and survival but not on quality of life and body weight in patients with cancer. As a limited number of high-quality studies were included, our findings highlight the need for more well-designed RCTs to further explore the benefits of HMB supplementation in patients with cancer.
| Studies | N (Sample Size) | Evidence | Summary of Findings |
|---------|----------------|----------|---------------------|
| Sanz-Paris 2018 [15] | 9 (1333) | N | Community dwelling older adults:  
Body composition: 1/3 studies showed improvement in body composition  
Muscle strength:  
Hand grip Strength: 1/3 studies showed improvement  
PT isokinetic flexion and extension: 1/1 studies show improvement  
PT isometric strength: 1/1 studies showed improvement  
Leg strength: 0/1 studies showed improvement  
|  | Insufficient evidence to determine | Insufficient evidence to determine | Some evidence in favour of no difference |
|  | 1 | “Data suggest a positive effect of HMB supplementation on muscle mass. No clear effect has been reported on muscle strength and physical performance.” | 1 | Yes |
| **Physical function:** | **Insufficient evidence to determine** |
|------------------------|--------------------------------------|
| 6-Minute Walking test: 1/1 studies showed improvement | Insufficient evidence to determine |
| *no significant difference between groups for total SPPB scores* | Insufficient evidence to determine |
| Sf 36 QoL: 1/1 studies showed improvement | Insufficient evidence to determine |
| *no significant difference in any other QoL measure (0/1)* | Insufficient evidence to determine |
| **Patients in peri-hospitalization setting:** | Some evidence in favour of no difference |
| Body composition: 2/5 studies showed improvement | Some evidence in favour of no difference |
| **Muscle strength:** 2/3 studies showed improvement | Some evidence in favour of intervention |
| **Physical function:** 1/2 studies showed improvement | Insufficient evidence to determine |
| Reference   | Study ID | Study Design | Study Findings                                                                 | Effect Size | Overall Conclusion                                                                 | Rating | Conflict of Interest |
|-------------|----------|--------------|--------------------------------------------------------------------------------|-------------|------------------------------------------------------------------------------------|--------|---------------------|
| Wu 2015 [16] | 6* (287) | Y            | Muscle mass: “the meta-analysis of muscle mass outcome showed increased muscle gain in the intervention groups than in the control groups” (SMD = 0.352 kg; 95% CI: 0.11, 0.594; z = 2.85; P = 0.004; I² = 0.0%; P = 0.438). | Some evidence in favour of intervention | “Overall, this meta-analysis indicates that HMB can prevent lean body mass loss in older adults. But the effects of HMB on muscle strength and physical function appears to vary in different populations.” | 5      | No                  |
|             | 6* (287) | Y            | Fat mass: “no statistically significant changes in fat mass outcomes between intervention and control groups” (SMD = -0.08 kg; 95% CI: -0.32, 0.159; z = 0.66; P = 0.511; I² = 0.0%; P = 0.741). | Some evidence in favour of no difference |                                                                      |        |                     |
| 5* (238)    | N        |              | Muscle strength: 3/6 studies showed improved muscle strength. Two of these studies looked HMB supplementation alone and one looked at HMB supplementation in combination with resistance exercise training. | Insufficient evidence |                                                                      | 2      |                     |
| 4 (214)     | N        |              | Physical function: 2/4 studies showed improved functionality | Insufficient evidence |                                                                      | 2      |                     |

*Outcomes are underlined.

*Stout et al. 2013 [17] is reported as one article; however, this article contains two phases; each phase is treated as their own study under results/findings, as each phase uses a unique set of participants.

Paper specific conflicts of interest are listed in separate table.

Abbreviations: ?, the number of studies was not mentioned in the systematic review/meta-analysis; body composition; AIDS, acquired immunodeficiency syndrome; CaHMB, calcium beta-hydroxy-beta-methylbutyrate; CI, confidence interval; COPD, chronic obstructive pulmonary
disease; EAA, essential amino acid; ES, effect size; FFM, fat-free mass; HMB, b-hydroxy-b-methylbutyrate; LSTM, lean soft tissue mass; MA, meta-analysis; MD, mean difference; NS, non-significant; PT, peak torque; QoE, quality of evidence; QoL, Quality of Life; Sf 36, Short Form 36 Health Survey Questionnaire; SMD, standardized mean difference; SPPB, short physical performance battery; TUG, Timed Up and Go test.
**Supplementary Table 4 - Papers screened, but not included and reason for exclusion**

| Author and reference | Type of Paper | Conclusion | Reason for exclusion |
|----------------------|---------------|------------|----------------------|
| Beaudart C, 2018 [18]| Conference abstract | “In conclusion, physical exercise has a beneficial impact on muscle mass, muscle strength or physical performance in healthy subjects aged 60 years and older. However, the additional effect of dietary supplementation has only been reported in a limited number of studies. For the majority of studies included in this systematic review, the population was composed of healthy older subjects. Studies assessing the impact of a combined exercise intervention and dietary intervention are still lacking in frail and sarcopenic populations, populations suffering from nutritional deficiency or populations at risk of malnutrition.” | Conference abstract |
| Burgess LC, 2018 [19]| Systematic Review | “There is limited evidence for nutritional supplementation in support of patients undergoing total hip replacement and total knee replacement; however, the low risk profile and potential benefits to adjunctive treatment methods, such as exercise programs, suggest certain supplements could play a role in enhancing recovery. Optimizing nutritional status pre-operatively may help manage the surgical stress response, and accelerate their turn to function for THR and TKR patients, with a particular benefit for undernourished, frail, or elderly individuals.” | Wrong target population (injured/pre-op patients) |
| Deutz NE, 2016 [20]| Randomized Control Trial | Although no effects were observed for the primary composite endpoint, compared with placebo HP-HMB decreased mortality and improved indices of nutritional status during the 90-day observation period. | Not a systematic review |
| Author(s) | Study Type | Summary | Notes |
|-----------|-------------|---------|-------|
| Fernández-Landa J, 2019 [21] | Systematic Review | “In summary, the combination of 3–10 g/day of CrM plus 3 g/day of HMB for 1–6 weeks could produce potential positive effects on sport performance (strength and anaerobic performance) and for 4 weeks on body composition (increasing fat free mass and decreasing fat mass). However, this combination seems to not show positive effects relating to markers of exercise-induced muscle damage and anabolic-catabolic hormones.” | Wrong target population (young healthy adults) |
| Gielen E, 2021 [1] | Umbrella Review | “Data suggest a positive effect of HMB supplementation on muscle mass. No clear effect has been reported on muscle strength and physical performance” | Not a systematic review |
| Goisser S, 2019 [22] | Conference abstract | “An up-to-date high-quality systematic review and meta-analysis may influence evidence-based treatment decisions and will help to identify knowledge gaps.” | Conference abstract |
| Hickson M, 2015 [23] | Narrative Review | “Overall, these data are suggestive of a beneficial effect of HMB on older adults, but larger well-controlled studies are required that measure outcomes relevant to sarcopenia, ideally in sarcopenic populations.” | Not a systematic review |
| Holland BM, 2019 [24] | Systematic Review and Meta-analysis | “In conclusion, the primary finding of this analysis suggests a small, nonsignificant effect of HMB on FFM in athletic populations. In agreement with previous research, HMB supplementation in athletes fails to alter BM while having a small, nonsignificant effect on FM. The positive effects of HMB on FFM and FM appear to diminish when protein intake is adequate (.1.6 g·kg⁻¹·d⁻¹) based on the limited current evidence.” | Wrong target population (young healthy adults) |
| Author(s) | Year | Study Type | Summary | Notes |
|-----------|------|------------|---------|-------|
| Jakubowski JS, 2020 [25] | Systematic Review and Meta-analysis | “HMB produces a small effect on TBM gain, but this effect does not translate into significantly greater increases in FFM, strength or decreases in FM during periods of RET. Our findings do not support the use of HMB aiming at improvement of body composition or strength with RET.” | Wrong target population (young healthy adults) |
| Kaczka P, 2019 [26] | Systematic Review | “HMB is among the supplements, which can be recommended for all sport disciplines regardless of sex and age. HMB supplementation reduces post exercise muscle damage, and thus accelerates recovery. It also allows for increases in lean body mass, improved strength and aerobic capacity.” | Wrong target population (young healthy adults) |
| Nunes EA, 2020 [27] | Conference abstract | “We conclude that HMB produces a small effect on TBM gain, but this effect does not translate into significantly greater increases in FFM, strength or decreases in FM during periods of RET. Our findings do not support the use of HMB aiming at improvement of body composition or strength with RET.” | Conference abstract |
| Oktaviana J, 2020 [28] | Systematic Review and Meta-analysis | “Protein supplementation alone does not significantly improve muscle mass, strength or function in pre-frail or frail older people.” | Wrong intervention |
| Rahimi MH, 2018 [29] | Systematic Review and Meta-analysis | “The current evidence revealed a time-dependent effect of HMB in reducing LDH and CK serum levels among adults. HMB, therefore, may be seen as a priority muscle damage recovery agent in interventions.” | Wrong outcome measures |
| Rocha-Rodriguez LG, 2019 [30] | Narrative Review | NF | Not a systematic review |
| Reference                                      | Study Type                  | Summary                                                                 | Notes                                           |
|------------------------------------------------|-----------------------------|------------------------------------------------------------------------|------------------------------------------------|
| Sanchez-Martinez J, 2018 [31]                  | Systematic Review and Meta-analysis | “No effect of HMB supplementation on strength and body composition in trained and competitive athletes” | Wrong target population (young healthy adults) |
| Silva VR, 2017 [32]                            | Systematic Review           | “In conjunction with resistance training, HMB-FA supplementation may attenuate markers of muscle damage, augment acute immune and endocrine responses, and cause increases in lean body mass, muscle hypertrophy, strength, and power in resistance trained men. HMB-FA supplementation may also improve markers of aerobic fitness when combined with high-intensity interval training” | Wrong target population (young healthy adults) |
| Testa G, 2020 [33]                             | Systematic Review           | “Sarcopenia is a physiological condition and contributes to the increased risk of falls and hip fractures in the older population. However, the diagnosis of sarcopenia is challenging, especially in hip-fractured patients, and there are currently no standardised diagnostic and therapeutic protocols. The development of medical management programs is mandatory for good prevention. To ensure adequate resource provision, care models should be reviewed, and new welfare policies should be adopted in the future.” | Wrong intervention |
| Valdés-Badilla P, 2021 [34]                    | Systematic Review           | “Olympic combat sports interventions (i.e., boxing, judo, karate, and taekwondo) improve older adults’ physical-functional, physiological, and psychoemotional health. Our systematic review confirms that OCS training has high adherence (greater than 80%) in older adults.” | Wrong intervention |
| van der Aa HPA, 2013 [35]                      | Randomized Control Trial    | “The importance and strengths of this study outweigh the challenges. The development and research of the | Not a systematic review |
| Reference          | Study Type       | Summary                                                                 | Notes                      |
|--------------------|------------------|-------------------------------------------------------------------------|----------------------------|
| Wandrag L, 2015 [36] | Systematic Review | “Overall, the data from ICU studies are very limited but suggest that HMB may improve nitrogen balance, although this improvement was marginal.” | Wrong outcome measures     |
## Supplementary table 5 - Conflicts of interest and sources of funding reported by the systematic reviews included in the analysis

| Reference            | Declared Conflicts of Interest                                                                                                                                                                                                 | Sources of Funding                                                                                                                                                                                                                                                                                                                                 |
|----------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Bear et al. [2]      | “DEB reports receiving advisory board fees, speaker fees and conference attendance support from Nutricia, Nestle Nutrition, BBraun, Baxter healthcare, Fresenius Kabi, and Abbott Nutrition. LW reports conference attendance support from Fresenius Kabi. AL, ED, SDRH, NH, BC, and KW report no conflicts of interest.” | “DEB is funded by a National Institute of Health Research (NIHR) and Health Education England (HEE) ICA Clinical Doctoral Research Fellowship (ICA-CDRF-2015-01-047). BC is funded by an NIHR Postdoctoral Fellowship (PDF-2015-08-015). This article presents independent research funded by the National Institute for Health Research (NIHR) and Health Education England. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.” |
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