Podiatric Physician's Guide to Protein and supplements in Regenerative and Functional Medicine

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No conflict of interest

Proteins

- Large complex molecules made up to long chains of amino acids

- Proteins are part of 4 major macromolecules
  - Carbohydrates
  - Lipids
  - Nucleic Acids

- Amino acid sequence determines the shape and function

Physiologic Importance of Proteins

- Structural and mechanical roles
- Enzymatic and metabolic roles
- Transport and storage
- Signaling and regulatory functions
- Immune defense
- Nutritional and developmental roles

Important Proteins

Hemoglobin

Actin and Myosin

Collagen

Insulin

Enzymes

Antibodies

9 Essential Amino Acids

Histidine

Isoleucine

Leucine

Lysine

Methionine

Phenylalanine

Threonine

Tryptophan

Valine

Muscle Mass and Proteins

What decreases muscle mass?

1. Anabolic Resistance
2. Sarcopenia
3. Chronic Inflammation or Illness
4. Insulin Resistance
5. Inadequate Intake
6. Physical Activity
7. Hormonal Changes

Maintaining Muscle Mass

1. Protein intake

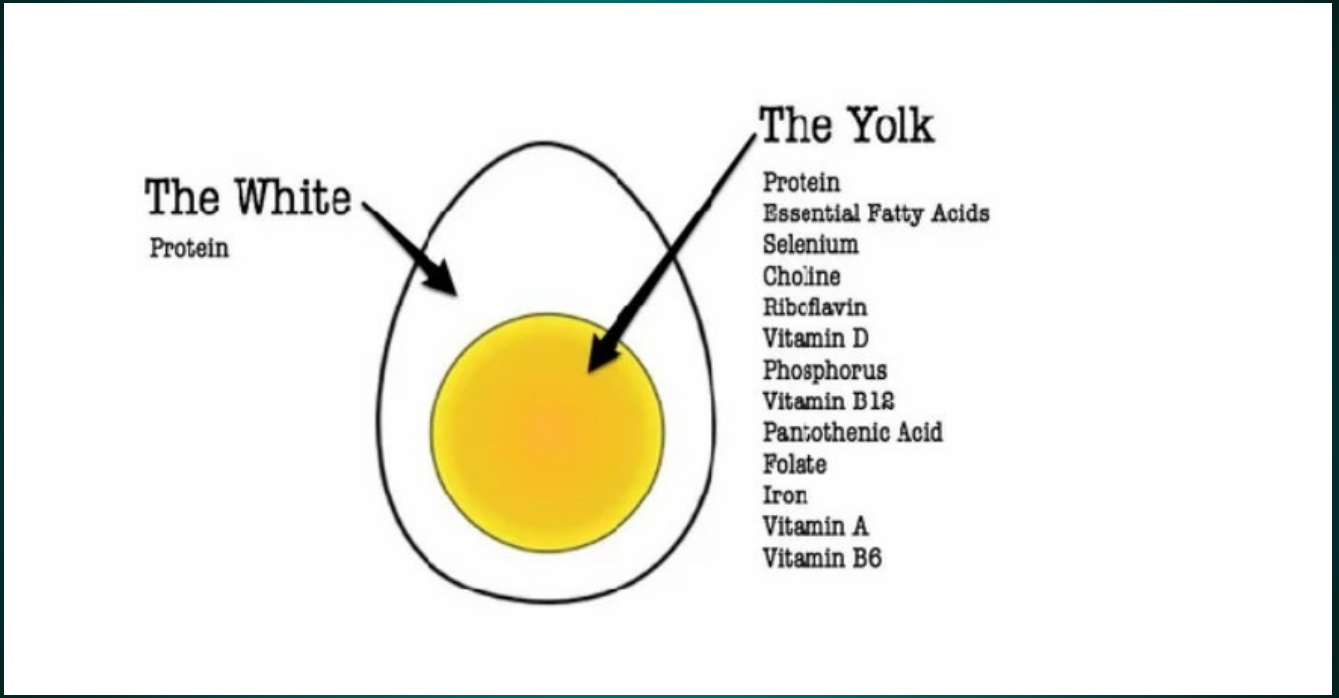
1. Leucine Threshold

    a. 1 gram of protein
        Per pound of body weight

    a. 3-5 grams of leucine daily

Protein + Leucine + Resistance Exercise

Breakfast


The White
Protein
The Yolk
Protein
Essential Fatty Acids
Selenium
Choline
Riboflavin
Vitamin D
Phosphorus
Vitamin B12
Pantothenic Acid
Folate
Iron
Vitamin A
Vitamin B6

A focus on leucine in the nutritional regulation of human skeletal muscle metabolism in ageing, exercise and unloading states

Isabel A Ely[1], Bethan E Phillips[1], Kenneth Smith[1], Daniel J Wilkinson[1], Mathew Piasecki[1], Leigh Breen[2], Mads S Larsen[3], Philip J Atherton[4]
Affiliations Expand

- 10.1016/j.clnu.2023.08.010

Abstract

Muscle protein synthesis (MPS) and muscle protein breakdown (MPB) are influenced through dietary protein intake and physical (in)activity, which it follows, regulate skeletal muscle (SKM) mass across the lifespan. Following consumption of dietary protein, the bio-availability of essential amino acids (EAA), and primarily leucine (LEU), drive a transient increase in MPS with an ensuing refractory period before the next MPS stimulation is possible (due to the "muscle full" state). At the same time, MPB is periodically constrained via reflex insulin actions. Layering exercise on top of protein intake increases the sensitivity of SKM to EAA, therefore extending the muscle full set-point (~48 h), to permit long-term remodelling (e.g., hypertrophy). In contrast, ageing and physical inactivity are associated with a premature muscle full set-point in response to dietary protein/EAA and contractile activity. Of all the EAA, LEU is the most potent stimulator of the mechanistic target of rapamycin complex 1 (mTORC1)-signalling pathway, with the phosphorylation of mTORC1 substrates increasing ~3-fold more than with all other EAA. Furthermore, maximal MPS stimulation is also achieved following low doses of LEU-enriched protein/EAA, negating the need for larger protein doses. As a result, LEU supplementation has been of long term interest to maximise muscle anabolism and subsequent net protein accretion, especially when in tandem with resistance exercise. This review highlights current knowledge vis-à-vis the anabolic effects of LEU supplementation in isolation, and in enriched protein/EAA sources (i.e., EAA and/or protein sources with added LEU), in the context of ageing, exercise and unloading states.

Dietary fiber intake and all-cause and cause-specific mortality: An updated systematic review and meta-analysis of prospective cohort studies

Fatemeh Ramezani[1], Farzad Pourghazi[1], Maysa Eslami[1], Maryam Gholami[2], Nami Mohammadian Khonsari[3], Hanieh-Sadat Ejtahed[4], Bagher Larijani[5], Mostafa Qorbani[6]
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Abstract

Background: Accumulating evidence supports the effects of dietary fiber on the risk of non-communicable diseases (NCDs). However, there is no updated systematic review and meta-analysis that compares and pools the effect of different types of fiber on mortality.

Methods: In this systematic review and meta-analysis, all prospective cohort studies that evaluated the relationship between dietary fiber intake and all-cause or cause-specific mortality were included. The PubMed, SCOPUS, and Web of Science databases were searched up to October 2022. Data extraction and quality assessment were performed by two researchers independently. Heterogeneity between studies was assessed using Chi-square based test. Random/fixed effect meta-analysis was used to pool the hazard ratios (HR) or relative risks (RR) and 95 % confidence intervals (CI) for the association between different types of fiber and mortality.

Conclusion: This comprehensive meta-analysis provides additional evidence supporting the protective association between fiber intake and all-cause and cause-specific mortality rates showing a 23 % reduction.

Top 5(+) Supplements for Podiatry Patients

1. Magnesium
2. Creatine
3. Vit D3 K2
4. Zinc
5. Omega - 3

1. Fiber
2. Methylated B - Vitamins

Big Pharma

Magnesium

400 mg / day

Needed in more than 300 enzymatic reactions

Involved in:

- Blood pressure regulation
- Blood glucose control
- Nerve function
- Muscle function
- Protein synthesis
- Bone development
- DNA synthesis
- The production of the antioxidant → Glutathione

Challenges in the Diagnosis of Magnesium Status

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Abstract

Magnesium is a critical mineral in the human body and is involved in ~80% of known metabolic functions. It is currently estimated that 60% of adults do not achieve the average dietary intake (ADI) and 45% of Americans are magnesium deficient, a condition associated with disease states like hypertension, diabetes, and neurological disorders, to name a few. Magnesium deficiency can be attributed to common dietary practices, medications, and farming techniques, along with estimates that the mineral content of vegetables has declined by as much as 80□90% in the last 100 years. However, despite this mineral's importance, it is poorly understood from several standpoints, not the least of which is its unique mechanism of absorption and sensitive compartmental handling in the body, making the determination of magnesium status difficult. The reliance on several popular sample assays has contributed to a great deal of confusion in the literature. This review will discuss causes of magnesium deficiency, absorption, handling, and compartmentalization in the body, highlighting the challenges this creates in determining magnesium status in both clinical and research settings.

Magnesium

Greater Involvement:

- Magnesium is required for ribosome stability and function during translation
- As a cofactor for many kinases and phosphatases, impacting signaling pathways
- Influences insulin signaling and glucose uptake in tissue
- Contributes to bone quality + structure
- Modulates the HPA Axis

Creatine

5 - 10 g / day

1. Energy production in muscle + brain

   - Creatine combine with phosphate to form → Phosphocreatine
   - Phosphocreatine donates phosphate to adenosine diphosphate to regenerate ATP
   - Helps stabilize ATP during sudden increases in neuronal activity
   - Helps to buffering activity in the brain to support cognitive activity

Creatine

2. Osmotic regulation and cell volume
   - Helps regulate intracellular water content
   - Helps maintain cell volume which influences cellular activity

3. Neuroprotective and Antioxidant Roles
   - Reduces vulnerability to Ischemia or neurodegeneration
   - Reduces oxidative stress by ensuring stable ATP supply and supports mitochondrial function

Creatine

4. Muscle anabolic and adaptational effects

- Allows greater total workload
- Better recovery after a workout
- Improvement in lean mass when combined with resistance training
- Can augment glycogen storage in muscles when combined with carbohydrates

The effects of creatine supplementation on cognitive function in adults: a systematic review and meta-analysis

Chen Xu, Siyuan Bi, Wenxin Zhang, Lin Luo
Affiliations Expand

- **Background:** This study aimed to evaluate the effects of creatine monohydrate supplementation on cognitive function in adults and explore its potential role in preventing and delaying cognitive impairment-related diseases.

Methods: Following the PRISMA 2020 guidelines, a systematic review with meta-analysis was conducted. Randomized controlled trials (RCTs) published between 1993 and 2024 were retrieved from PubMed, Scopus, and Web of Science databases. The study protocol was registered with PROSPERO (registration number: CRD42024533557). The impact of creatine supplementation on overall cognitive function, memory, executive function, attention, and information processing speed was assessed using standardized mean differences (SMD) and Hedge's g with 95% confidence intervals (CI).

Conclusion: Current evidence suggests that creatine monohydrate supplementation may confer beneficial effects on cognitive function in adults, particularly in the domains of memory, attention time, and information processing speed. Larger robust clinical trials are warranted to further validate these findings. Furthermore, future research should investigate the influence of different populations and intervention durations on the effects of creatine monohydrate supplementation, as well as elucidate the precise mechanisms underlying its potential cognitive-enhancing properties.

Vit D3 K2

30 - 100 ng/mL

D3 = cholecalciferol

Importance:

1. Calcium and Phosphate Homeostasis
    - Enhances intestinal absorption of calcium + phosphate to support bone mineralization
    - Work with parathyroid hormone to maintain serum calcium level
    - Facilities mobilization of calcium from bone when dietary intake is low

Vit D3 K2

2. Bone Health
   - Improves muscle strength and function (helps reduce fall risks)
   - Essential for bone growth and remodelity

3. Immune Modulation
   - Influences innate and adaptive immune responses

4. Cell Differentiation
   - Acts as a secosteroid hormone that binds to Vitamin D receptor in many cells, affecting gene expression

Role of vitamin K_2 in bone metabolism: a point of view and a short reappraisal of the literature

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Abstract

Vitamin K_2 (vit K_2) belongs to a large group of fat-soluble compounds whose formulation is MK (menaquinone) (MK-2 to MK-14), that seem to be involved in different biological functions. In particular, vit K_2 has been recently recognized as efficacious and safe in treatment of bone loss, as it contributes to structural integrity of osteocalcin (OC), the major non-collagenous protein typically found in bone matrix. Several studies proved low vit K_2 intake is linked to bone loss and to increased fracture risk in both sexes. Nowadays, vit K_2 supplementation is considered a significant manner to enhance the association of calcium and vitamin D whose role on bone health is largely recognized. On the other hand, vit K_2 may be used alone or with other drugs to preserve bone quality/strength from skeletal degradation after menopause and/or in patients affected by secondary osteoporosis. In this paper, we review the most recent data about vit K_2 on skeleton.

Vit D3

Source: Sunlight (UVB) Exposure converts 7 - Dehydrocholesterol in skin to Vit D3

Dietary Sources - Fatty fish + supplements

Activation:

Vit D3 is hydroxylated in the liver to 25 - hydroxyvitamin D then in the kidneys to the active form

1, 25 - hydroxyvitamin D

VIT D3 K2 → 5,000 IU daily

Zinc

Key Role:

1. Catalytic and structural roles in enzymes
    - Acts as a cofactor for hundreds of enzymes involved in
        - Digestion
        - Metabolism
        - DNA Synthesis

    - Needed to properly function enzymes like carbonic anhydrase , alkaline phosphatase and dehydrogenase

Zinc

2. Gene expression and protein synthesis

- Needed for gene regulation and cellular growth
- Influences signaling pathways that control cell division, differentiation and apoptosis

3. Immune Function

- Supports development and function of immune cells
    - T + B cell, natural killer cells
- Important for maintaining skin + mucosal barriers
- Low levels impairs immune response

Zinc

4. Antioxidant and Anti-Inflammatory
   - Stabilizes cell membranes
   - Modulates inflammatory signaling

5. Protein synthesis and growth
   - Wound healing

6. Endocrine Function
   - Influences insulin storage and secretion on the pancreas
   - Plays a role in lipid and carbohydrate metabolism

7. Neurological
   - Modulates neurotransmitter signaling
   - Supports learning and memory

Randomized Controlled Trial

Wound Repair Regen

. 2017 May;25(3):512-520.
doi: 10.1111/wrr.12537. Epub 2017 May 9.

The effects of zinc supplementation on wound healing and metabolic status in patients with diabetic foot ulcer: A randomized, double-blind, placebo-controlled trial

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Abstract

This study was performed to determine the effects of zinc supplementation on wound healing and metabolic status in patients with diabetic foot ulcer. The current randomized, double-blind, placebo-controlled trial was conducted among 60 patients (aged 40-85 years old) with grade 3 diabetic foot ulcer. Participants were randomly divided into two groups (30 participants in each group) to take either 220 mg zinc sulfate supplements containing 50 mg elemental zinc or placebo daily for 12 weeks. mg/dl, p = 0.01), plasma total antioxidant capacity (+91.7 ± 213.9 vs. -111.9 ± 188.7 mmol/L, p < 0.01) and total glutathione (+68.1 ± 140.8 vs. -35.0 ± 136.1 μmol/L, p = 0.006), and significant decreases in high sensitivity C-reactive protein (-20.4 ± 24.6 vs. -6.8 ± 21.3 μg/ml, p = 0.02) and plasma malondialdehyde concentrations (-0.6 ± 0.9 vs. -0.2 ± 0.7 μmol/L, p = 0.03) were seen following supplementation with zinc compared with the placebo. Zinc supplementation for 12 weeks among diabetic foot ulcer patients had beneficial effects on parameters of ulcer size and metabolic profiles.

Omega - 3's

Omega - 3 fatty acids are polyunsaturated fats

Key Omega - 3's

Eicosapentaenoic Acid (EPA)

Docosahexaenoic Acid (DHA)

Omega - 3's

Major Roles of Omega - 3's

1. Cell membrane structure and function

- EPA + DHA are incorporated into cell membranes, affecting receptor function
- DHA is abundant in neuronal receptor function

2. Cardiovascular Health

- Can lower triglycerides
- Reduces vascular inflammation
- Affects platelet aggregation - modesty

Omega - 3's

3. Neurocognitive

- DHA important for brain development in infancy and cognitive function in adulthood
- EPA may help with mood disorders

4. Inflammation and Immune Function

- EPA and DHA give rise to specialized mediators that help resolve inflammation
- May benefit inflammatory conditions (Rheumatoid arthritis, inflammatory bowel disease)

Omega - 3's

5. Metabolic Health

- May improve insulin sensitivity and fatty acid oxidations

Effect of Omega-3 Dosage on Cardiovascular Outcomes: An Updated Meta-Analysis and Meta-Regression of Interventional Trials

Aldo A Bernasconi[1], Michelle M Wiest[2], Carl J Lavie[3], Richard V Milani[3], Jari A Laukkanen[4]

Abstract

Objectives: To quantify the effect of eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids on cardiovascular disease (CVD) prevention and the effect of dosage.

Methods: This study is designed as a random effects meta-analysis and meta-regression of randomized control trials with EPA/DHA supplementation. This is an update and expanded analysis of a previously published meta-analysis which covers all randomized control trials with EPA/DHA interventions and cardiovascular outcomes published before August 2019. The outcomes included are myocardial infarction (MI), coronary heart disease (CHD) events, CVD events (a composite of MI, angina, stroke, heart failure, peripheral arterial disease, sudden death, and non-scheduled cardiovascular surgical interventions), CHD mortality and fatal MI. The strength of evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation framework.

Results: A total of 40 studies with a combined 135,267 participants were included. Supplementation was associated with reduced risk of MI (relative risk [RR], 0.87; 95% CI, 0.80 to 0.96), high certainty number needed to treat (NNT) of 272; CHD events (RR, 0.90; 95% CI, 0.84 to 0.97), high certainty NNT of 192; fatal MI (RR, 0.65; 95% CI, 0.46 to 0.91]), moderate certainty NNT = 128; and CHD mortality (RR, 0.91; 95% CI, 0.85 to 0.98), low certainty NNT = 431, but not CVD events (RR, 0.95; 95% CI, 0.90 to 1.00). The effect is dose dependent for CVD events and MI.

Conclusion: Cardiovascular disease remains the leading cause of death worldwide. Supplementation with EPA and DHA is an effective lifestyle strategy for CVD prevention, and the protective effect probably increases with dosage.

Association of Serum Docosahexaenoic Acid With Cerebral Amyloidosis

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Affiliations Expand

Abstract

Importance: Higher dietary intake of the essential fatty acid docosahexaenoic (DHA) has been associated with better cognitive performance in several epidemiological studies. Animal and in vitro studies also indicate that DHA prevents amyloid deposition in the brain.

Objective: To determine the association between serum DHA levels, cerebral amyloidosis, and the volumes of brain areas affected by Alzheimer disease.

Design, settings, and participants: Cross-sectional analysis of serum DHA levels together with measures of amyloid deposition (Pittsburgh Compound B index), brain volumes, and neuropsychological testing scores from 61 participants in the Aging Brain Study. The study was conducted between June 2008 and May 2013, and the data were analyzed between October 2015 and April 2016. Linear models were adjusted for age, sex, years of education, and apolipoprotein E status.

Main outcomes and measures: Serum DHA levels with cerebral amyloidosis measured using PIB PET.

Results: Samples were available from 61 Aging Brain Study participants (41 women and 20 men) who underwent amyloid PET imaging. The mean (SD) age of the participants was 77 (6) years and ranged from 67 to 88 years. Serum DHA levels (percentage of total fatty acids) were 23% lower in participants with cerebral amyloidosis than those without (0.97 vs 1.25, P = .007) and were inversely correlated with brain amyloid load (r = -0.32, P = .01) independent of age, sex, apolipoprotein E genotype, and years of education. Moreover, greater serum DHA levels were positively associated with brain volume in several subregions affected by AD, in particular the left subiculum (r = 0.38, P = .005) and the left entorhinal volumes (r = 0.51, P = .001). Serum DHA levels were also associated with nonverbal memory scores (r = 0.28, P = .03).

Conclusions and relevance: In this study, serum DHA levels were associated with pathogenesis of cerebral amyloidosis and with preservation of entorhinal and hippocampal volumes. These findings suggest an important role for DHA metabolism in

Omega-3 Fatty acids for cardiovascular disease prevention

Andrew Paul Defilippis[1], Michael J Blaha, Terry A Jacobson
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Abstract

Major dietary sources of omega-3 fatty acids are fish containing eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), as well as nuts, seeds, and vegetable oils containing α-linolenic acid (ALA). Omega-3 fatty acids, especially those derived from marine sources, may be a useful tool for the primary and secondary prevention of cardiovascular disease. Omega-3s exert their cardioprotective effects through multiple mechanisms, including reducing arrhythmias and altering production of prostaglandins, which reduces inflammation and improves platelet and endothelial function. To date, no serious adverse effects of omega-3s have been identified, despite extensive study. In adults, any potential harm from mercury exposure from consuming fish rich in omega-3s is outweighed by the proven cardiovascular benefits of eating fish. Concerns over increased bleeding complications have not materialized despite the increased concomitant use of aspirin and clopidogrel. We recommend one serving (200-400 g) of fatty fish two times per week and a diet that includes foods rich in ALA for the primary prevention of cardiovascular disease. We recommend one serving (200-400 g) of fatty fish or a fish oil supplement containing 900 mg of EPA + DHA every day and a diet rich in ALA for patients with known cardiovascular disease or congestive heart failure.

Thank you

Effects of creatine supplementation on memory in healthy individuals: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Context: From an energy perspective, the brain is very metabolically demanding. It is well documented that creatine plays a key role in brain bioenergetics. There is some evidence that creatine supplementation can augment brain creatine stores, which could increase memory.

Objective: A systematic review and meta-analysis of randomized controlled trials (RCTs) was conducted to determine the effects of creatine supplementation on memory performance in healthy humans.

Data sources: The literature was searched through the PubMed, Web of Science, Cochrane Library, and Scopus databases from inception until September 2021.

Data extraction: Twenty-three eligible RCTs were initially identified. Ten RCTs examining the effect of creatine supplementation compared with placebo on measures of memory in healthy individuals met the inclusion criteria for systematic review, 8 of which were included in the meta-analysis.

Data analysis: Overall, creatine supplementation improved measures of memory compared with placebo (standard mean difference [SMD] = 0.29, 95%CI, 0.04-0.53; I2 = 66%; P = 0.02). Subgroup analyses revealed a significant improvement in memory in older adults (66-76 years) (SMD = 0.88; 95%CI, 0.22-1.55; I2 = 83%; P = 0.009) compared with their younger counterparts (11-31 years) (SMD = 0.03; 95%CI, -0.14 to 0.20; I2 = 0%; P = 0.72). Creatine dose (≈ 2.2-20 g/d), duration of intervention (5 days to 24 weeks), sex, or geographical origin did not influence the findings.

Conclusion: Creatine supplementation enhanced measures of memory performance in healthy individuals, especially in older adults (66-76 years).

The effects of creatine supplementation on cognitive function in adults: a systematic review and meta-analysis

Chen Xu, Siyuan Bi, Wenxin Zhang, Lin Luo
Affiliations Expand

Abstract

Background: This study aimed to evaluate the effects of creatine monohydrate supplementation on cognitive function in adults and explore its potential role in preventing and delaying cognitive impairment-related diseases.

Methods: Following the PRISMA 2020 guidelines, a systematic review with meta-analysis was conducted. Randomized controlled trials (RCTs) published between 1993 and 2024 were retrieved from PubMed, Scopus, and Web of Science databases. The study protocol was registered with PROSPERO (registration number: CRD42024533557). The impact of creatine supplementation on overall cognitive function, memory, executive function, attention, and information processing speed was assessed using standardized mean differences (SMD) and Hedge's g with 95% confidence intervals (CI).

Conclusion: Current evidence suggests that creatine monohydrate supplementation may confer beneficial effects on cognitive function in adults, particularly in the domains of memory, attention time, and information processing speed. Larger robust clinical trials are warranted to further validate these findings. Furthermore, future research should investigate the influence of different populations and intervention durations on the effects of creatine monohydrate supplementation, as well as elucidate the precise mechanisms underlying its potential cognitive-enhancing properties.