Protein

The Role of Protein Intake and Its Timing on Body Composition and Muscle Function in Healthy Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials


Significance: This review found support for a positive impact of protein supplementation on the lean body mass of adults, independent of intake timing.

Background: Increased protein intake has been suggested to improve gains in muscle mass and strength in adults. Furthermore, the timing of protein intake has been discussed as a margin of opportunity for improved prevention measures. Objective: This systematic review investigated the effect of protein supplementation on body composition and muscle function (strength and synthesis) in healthy adults, with an emphasis on the timing of protein intake. Methods: Randomized controlled trials were identified using PubMed, Web of Science, CINAHL, and Embase, up to March 2019. For meta-analyses, data on lean body mass (LBM), handgrip strength, and leg press strength were pooled by age group (mean age 18-55 or >55 y) and timing of protein intake. The quality of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluations approach. Results: Data from 65 studies with 2907 participants (1514 men and 1380 women, 13 unknown sex) were included in the review. Twenty-six, 8, and 24 studies were used for meta-analysis on LBM, handgrip strength, and leg press strength, respectively. The protein supplementation was effective in improving (mean difference; 95% CI) LBM in adults (0.62 kg; 0.36, 0.88) and older adults (0.46 kg; 0.23, 0.70), but not handgrip strength (older adults: 0.26 kg; -0.51, 1.04) and leg press strength (adults: 5.80 kg; -0.33, 11.93; older adults: 1.97 kg; -2.78, 6.72). Sensitivity analyses removing studies without exercise training had no impact on the outcomes. Data regarding muscle synthesis were scarce and inconclusive. Subgroup analyses showed no beneficial effect of a specific timing of protein intake on LBM, handgrip strength, and leg press strength. Conclusion: Overall, the results support the positive impact of protein supplementation on LBM of adults and older adults, independently of intake timing. Effects on muscle strength and synthesis are less clear and need further investigation.

Carnosine and Histidine-Containing Dipeptides Improve Dyslipidemia: A Systematic Review and Meta-Analysis of Randomized Controlled Trials


Significance: A meta-analysis of 18 studies found that histidine-containing dipeptides may improve lipid profiles by lowering total cholesterol and triglyceride levels.

Context: Cardiovascular disease is a major public health problem and represents a significant burden of disease globally. Lifestyle interventions have their limitations and an intervention that will effectively address cardiovascular risk factors to help
reduce this growing burden of disease is required. **Objective:** Carnosine and other histidine-containing dipeptides (HCDs) have exerted positive effects on cardiovascular risk factors and diseases in animal and human studies. The authors conducted a systematic review and meta-analysis examining the effects of HCDs on cardiovascular outcomes in line with the PRISMA guidelines. **Data sources:** The Medline, Medline in process, Embase, Cumulative Index of Nursing and Allied Health, and All EBM databases were searched from inception until January 25, 2019, for randomized controlled trials (RCTs) examining the effects of HCDs on cardiovascular outcomes, compared with placebo or controls. **Data extraction:** Basic characteristics of the study and populations, interventions, and study results were extracted. The grading of recommendations assessment, development, and evaluation approach was used to assess the quality of evidence for each outcome. **Data analysis:** A total of 21 studies were included. Of these, 18 were pooled for meta-analysis (n = 913). In low risk of bias studies, HCD-supplemented groups had lower total cholesterol (n = 6 RCTs; n = 401; weighted mean difference \[WMD\], -0.32 mmol/L [95%CI, -0.57 to -0.07], \(P = 0.01\)) and triglyceride levels (n = 6 RCTs; n = 401; \(WMD, -0.14 \text{ mmol/L [95\%CI, -0.20 to -0.08],}\) \(P < 0.001\)) compared with controls. In studies using carnosine alone, triglycerides levels were also lower in the intervention group vs controls (n = 5 RCTs; n = 309; \(P < 0.001\)). There were no significant differences in blood pressure, heart rate, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol (HDL-C) or the total cholesterol to HDL-C ratio between groups. **Conclusions:** Carnosine and other HCDs may have a role in improving lipid profiles. Larger studies with sufficient follow-up are necessary to confirm these findings and explore the use of HCDs in the prevention of cardiovascular diseases.

**Lipids**

**Consumption of Fish and \(\omega-3\) Fatty Acids and Cancer Risk: An Umbrella Review of Meta-Analyses of Observational Studies**


**Significance:** A meta-analysis of observational studies found weak associations between \(\omega-3\) fatty acid intake and risk of only some cancer types.

Multiple studies have suggested that \(\omega-3\) fatty acid intake may have a protective effect on cancer risk; however, its true association with cancer risk remains controversial. We performed an umbrella review of meta-analyses to summarize and evaluate the evidence for the association between \(\omega-3\) fatty acid intake and cancer outcomes. We searched PubMed, Embase, and the Cochrane Database of Systematic Reviews from inception to December 1, 2018. We included meta-analyses of observational studies that examined associations between intake of fish or \(\omega-3\) fatty acid and cancer risk (gastrointestinal, liver, breast, gynecologic, prostate, brain, lung, and skin) and determined the level of evidence of associations. In addition, we appraised the quality of the evidence of significant meta-analyses by using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. We initially screened 598 articles, and 15 articles, including 57 meta-analyses, were eligible. Among 57 meta-analyses, 15 reported statistically significant results. We found that 12 meta-analyses showed weak evidence of an association between \(\omega-3\) fatty acid intake and risk of the following types of cancer: liver cancer (n = 4 of 6), breast cancer (n = 3 of 14), prostate cancer (n = 3 of 11), and brain tumor (n = 2 of 2). In the other 3 meta-analyses, studies of endometrial cancer and skin cancer, there were no assessable data for determining the evidence levels. No meta-analysis showed convincing, highly suggestive, or suggestive evidence of an association. In the sensitivity analysis of meta-analyses by study design, we found weak associations between \(\omega-3\) fatty acid intake and breast cancer risk in cohort studies, but no statistically significant association in case-control studies. However, the opposite results were found in case of brain tumor risk. Although \(\omega-3\) fatty acids have been studied in several meta-analyses with regard to a wide range of cancer outcomes, only weak associations were identified in some cancer types, with several limitations. Considering the nonsignificant or weak evidence level, clinicians and researchers should cautiously interpret reported associations between \(\omega-3\) fatty acid consumption and cancer risks.

**Carbohydrates**

**Added Sugar and Sugar-Sweetened Beverages Are Associated With Increased Postpartum Weight Gain and Soluble Fiber Intake Is Associated With Postpartum Weight Loss in Hispanic Women From Southern California**


**Significance:** Consumption of sugar-sweetened beverages was associated with postpartum weight gain—and consumption of soluble fiber with postpartum weight loss—in Hispanic women.
**Background:** Obesity prevalence remains high in the United States, and there is an increased risk among women who do not lose their gestational weight gain during the postpartum period. Indicators of dietary carbohydrate quality including added sugar consumption, glycemic load, and glycemic index have been linked with weight gain, whereas fiber may protect against obesity. However, these dietary factors have not been examined during the postpartum period. **Objectives:** The aim of this study was to determine whether dietary sugars and fiber intake were associated with changes in postpartum weight. **Methods:** We examined Hispanic women from the longitudinal Southern California Mother’s Milk Study (n = 99) at 1 and 6 mo postpartum. Maternal assessments included height, weight, and dietary intake based on 24-h diet recalls. We used multivariable linear regression to examine the relation between maternal diet and change in postpartum weight after adjusting for maternal age, height, and energy intake. **Results:** Higher intake of added sugar was associated with postpartum weight gain (β: 0.05; 95% CI: 0.004, 0.10; P = 0.05). In addition, a half 8-ounce (8 fluid ounces = 236.6 mL) serving per day increase in soft drinks was associated with a 1.52-kg increase in weight (95% CI: 0.70, 2.34 kg; P < 0.001). A high glycemic index (β: 0.25; 95% CI: 0.07, 0.42; P = 0.006) and glycemic load (β: 0.04; 95% CI: 0.002, 0.08; P = 0.04) were associated with postpartum weight gain. Higher soluble fiber was associated with a decrease in postpartum weight (β: -0.82 kg; 95% CI: -1.35, -0.29 kg; P = 0.003) and the negative effects of added sugar, sugary beverages, and high-glycemic-index and -load diets were partially attenuated after adjusting for soluble fiber intake. **Conclusions:** Increased consumption of added sugar, sugar-sweetened beverages, and high-glycemic diets were associated with greater weight gain in the first 6 mo postpartum. In addition, increased consumption of soluble fiber was associated with postpartum weight loss, which may partially offset the obesogenic effects of some dietary sugars.

**Effect of Glucose and Sucrose on Cognition in Healthy Humans: A Systematic Review and Meta-Analysis of Interventional Studies**


**Significance:** A limited body of evidence supports the hypothesis that glucose consumption improves the performance of immediate verbal tasks.

**Context:** Evidence suggests that plasma glucose levels may influence cognitive performance, but this has not been systematically reviewed and quantified. **Objective:** The aim of this review was to investigate the potential effects of glucose and sucrose, compared with placebo, on cognition in healthy humans. **Data sources:** The electronic databases PubMed and Web of Science were searched up to December 2019. Reference lists of selected articles were checked manually. **Study selection:** Randomized controlled trials or crossover trials that compared glucose or sucrose with placebo for effects on cognition were eligible. **Data extraction:** Potentially eligible articles were selected independently by 2 authors. Risk of bias was assessed through the Cochrane Collaboration tool. Standardized mean differences (SMDs) were obtained from random-effects meta-analyses for a subsample of studies that reported the same outcomes. **Results:** Thirty-seven trials were identified, of which 35 investigated the effect of glucose consumption compared with placebo on cognition. Two studies found no effect of glucose on cognition, while the others found mixed results. Only 3 of the 37 studies investigated the effects of sucrose intake, reporting mixed results. Meta-analyses revealed a significantly positive effect of glucose compared with control, but only when a verbal performance test (immediate word recall) was used in parallel-design studies (SMD = 0.61; 95%CI, 0.20-1.02; I² = 0%). Twenty-four studies were classified as having high risk of bias for the selection procedure. **Conclusions:** A limited body of evidence shows a beneficial effect of glucose in individuals performing immediate verbal tasks. High-quality trials with standardized cognitive measurements are needed to better establish the effect of glucose or sucrose on cognition.

**Low-Calorie Sweeteners**

**Current Progress in Understanding the Structure and Function of Sweet Taste Receptor**


**Significance:** This review highlights current knowledge on the structure, function, genetics and evolution of the sweet taste receptor, which may be helpful guidance for personalized feeding, diet and medicine.

The sweet taste receptor, which was identified approximately 20 years ago, mediates sweet taste recognition in humans and other vertebrates. With the development of genomics, metabolomics, structural biology, evolutionary biology, physiology, and neuroscience, as well as technical advances in these areas, our understanding of this important protein has resulted in substantial progress. This article reviews the structure, function, genetics, and evolution of the sweet taste receptor and offers meaningful insights into this G protein-coupled receptor, which may be helpful guidance for personalized feeding, diet and medicine. Prospective directions for research on sweet taste receptors have also been proposed.
Consumption of the Artificial Sweetener Acesulfame Potassium Throughout Pregnancy Induces Glucose Intolerance and Adipose Tissue Dysfunction in Mice


**Significance:** Consumption of high-fructose corn syrup and acesulfame potassium was associated with maternal metabolic dysfunction in mice.

**Background:** Sugar-sweetened beverage consumption is associated with metabolic dysfunction. Artificially sweetened beverages (ASBs) are often promoted as an alternative. However, evidence for the safety of ASB consumption during pregnancy is lacking. **Objectives:** The effects of sugar-sweetened beverage and ASB consumption during pregnancy in mice were examined, and we hypothesized that both sugar-sweetened beverages and ASBs would impair maternal metabolic function. **Methods:** Pregnant female C57BL/6J mice received control drinking water (CD), high-fructose corn syrup (Fr; 20% kcal intake; 335 mM), or the artificial sweetener acesulfame potassium (AS; 12.5 mM) in their drinking water, from gestational day (GD) 0.5 (n = 8/group). Body weights and food and water intakes were assessed every second day, an oral-glucose-tolerance test (OGTT) was performed at GD 16.5, and mice were culled at GD 18.5. RT-PCR was carried out on adipose tissue, liver, and gut. Adipose tissue morphology was assessed using histological methods. In a separate cohort of animals, pregnancy length was assessed. Repeated-measures ANOVA was performed for the OGTT and weight gain data. All other data were analyzed by 1-way ANOVA. **Results:** Fr and AS significantly impaired glucose tolerance, as demonstrated by OGTT (21% and 24% increase in AUC, respectively; P = 0.0006). Fr and AS reduced expression of insulin receptor (39.5% and 33% reduction, respectively; P = 0.02) and peroxisome proliferator-activated receptor γ (45.2% and 47%, respectively; P = 0.039), whereas Fr alone reduced expression of protein kinase B (36.9% reduction; P = 0.048) and resulted in an increase in adipocyte size and leptin concentrations (40% increase; P = 0.03). AS, but not Fr, reduced male fetal weight (16.5% reduction; P = 0.04) and female fetal fasting blood glucose concentration at cull (20% reduction; P = 0.02) compared with CD. AS significantly reduced the length of pregnancy compared with the CD and Fr groups (1.25 d shorter; P = 0.02). **Conclusions:** Fr and AS consumption were associated with maternal metabolic dysfunction in mice. AS was also associated with reduced fetal growth and fetal hypoglycemia. Therefore, ASBs may not be a beneficial alternative to sugar-sweetened beverages during pregnancy.

Bioactives

Flavonoid Intake and MRI Markers of Brain Health in the Framingham Offspring Cohort


**Significance:** Data suggest that higher flavonoid intakes may affect dementia risk in middle-aged and older adults by reducing white matter volume in the brain—a marker associated with Alzheimer’s disease and related dementias.

**Background:** Although greater flavonoid intake is associated with a reduced risk of Alzheimer’s disease (AD) and related dementias (ADRD), evidence relating dietary flavonoid intake to brain health based on MRI is lacking. **Objective:** The objective of this study was to explore the association between dietary flavonoid intake and MRI measures of brain health, including total brain tissue volume (TBV), white matter hyperintensities volume (WMHV), and hippocampal volume (HV). **Methods:** Eligible subjects included members of the Framingham Heart Study Offspring Cohort who were free of stroke at exam 7 and had at least 1 valid food frequency questionnaire from exams 5, 6, or 7 (n = 2086; mean age at exam 7, 60.6 y). Flavonoid intakes represented the cumulative mean of intakes across the 3 exams and were categorized based on quartiles categories of intake. TBV, WMHV, and HV were assessed at exam 7. Multiple linear regression models were used to examine the cross-sectional association between total and the 6 classes of flavonoids and the 3 aforementioned MRI measures. **Results:** The mean (95% CI) of the WMHV of subjects in the highest quartile category of flavan-3-ols [0.56 (0.52, 0.61)] and flavonoid polymers [0.57 (0.52, 0.61)] intake was significantly smaller relative to that of subjects in the lowest quartile category of flavan-3-ols [0.65 (0.60, 0.71)] and flavonoid polymers [0.66 (0.60, 0.71)] after accounting for important demographic, lifestyle, and clinical factors. Inverse trend associations with WMHV were also seen for flavan-3-ols (P = 0.01) and flavonoid polymers (P = 0.01) as well as for total flavonoids (P = 0.01). TBV and HV were not associated with dietary flavonoid intake following the adjustment for potential confounders. **Conclusions:** Our results contribute to the literature on flavonoids and ADRD as they suggest that higher flavonoid intakes may affect ADRD risk in middle-aged and older adults by reducing WMHV, a marker strongly associated with ADRD.
Sodium

Associations of 24-Hour Urinary Sodium and Potassium Excretion With Cardiac Biomarkers: The Maastricht Study


Significance: This study found a nonlinear association between lower urinary potassium excretion and two markers of cardiomyocyte injury and cardiac dysfunction, suggesting cardiac dysfunction and/or cardiomyocyte injury may underlie previously reported associations of lower potassium intake with CVD mortality.

Gut Microbiome

Neonatal Diet Alters Fecal Microbiota and Metabolome Profiles at Different Ages in Infants Fed Breast Milk or Formula


Significance: Breastfeeding, dairy-based formula and soy-based formula differentially impact the infant fecal microbiome and metabolome in the first year of life.

Background: Neonatal diet has a large influence on child health and might modulate changes in fecal microbiota and metabolites. Objectives: The aim is to investigate fecal microbiota and metabolites at different ages in infants who were breastfed (BF), received dairy-based milk formula (MF), or received soy-based formula (SF).

Methods: Fecal samples were collected at 3 (n = 16, 12, and 14, respectively), 6 (n = 20, 19, and 15, respectively), 9 (n = 12, 11, and 12, respectively), and 12 mo (n = 14, 14, and 15, respectively) for BF, MF, and SF infants. Infants that breastfed until 9 mo and switched to formula were considered as no longer breastfeeding at 12 mo. Microbiota data were obtained using 16S ribosomal RNA sequencing. Untargeted metabolomics was conducted using a Q-Exactive Hybrid Quadrupole-Orbitrap mass spectrometer. The data were analyzed using R (version 3.6.0) within the RStudio (version 1.1.463) platform.

Results: At 3, 6, and 9 mo of age BF infants had the lowest α-diversity, SF infants had the highest diversity, and MF was intermediate. Bifidobacterium was 2.6- to 5-fold lower in SF relative to BF infants through 1 y of life. An unidentified genus from Ruminococcaceae higher in the SF (2%) than in the MF (0.4%) and BF (0.08%) infants at 3 mo of age was observed. In BF infants higher levels of butyric acid, d-sphingosine, kynurenic acid, indole-3-lactic acid, indole-3-acetic acid, and betaine were observed than in MF and SF infants. At 3 mo Ruminococcaceae was positively correlated to azelaiac, gentisic, isocitric, sebacic, and syringic acids. At 6 mo Oscillospira was negatively correlated with 3-hydroxybutyric acid, hydroxy-hydrocinnamic acid, and betaine whereas Bifidobacterium was negatively associated with 5-hydroxytryptamine. At 12 mo of age, Lachnospiraceae was negatively associated with hydroxyphenyllactic acid. Conclusions: Infant diet has a large impact on the fecal microbiome and metabolome in the first year of life.
Probiotics for Dementia: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

**Significance:** This meta-analysis found insufficient information to support clinical application of probiotics and synbiotics to improve cognitive function in people with dementia.

**Context:** Dementia is the fifth leading cause of death in the world. Animal studies indicate that in addition to the aging process, intestinal microbiota may play an important role in the neurodegeneration process through the modulation of the gut-brain axis. **Objective:** A systematic review and meta-analysis was conducted to determine the effectiveness of probiotic and synbiotic supplementation on the cognitive function of individuals with dementia. **Data sources:** MEDLINE, BVS, SciELO, CENTRAL, Embase, and grey literature were searched from their inception to January 2019. **Study selection:** We included data from randomized clinical trials (RCTs) that addressed dementias and assessed the following outcomes: cognitive function; inflammatory, oxidative stress, and metabolic markers; nutritional status; and intestinal microbiota composition. **Data extraction:** Data searches, article selection, data extraction, and risk-of-bias assessments were performed according to the Cochrane guidelines. Data were pooled by inverse-variance random-effects meta-analyses. **GRADE** (Grading of Recommendations Assessment, Development, and Evaluations) was used to assess the quality of evidence. **Results:** Data from 3 RCTs involving 161 individuals with Alzheimer’s disease receiving *Lactobacillus* and *Bifidobacterium* strains showed no beneficial effect of probiotic supplementation on cognitive function (standardized mean difference, 0.56; 95%CI: -0.06 to 1.18), with very low certainty of evidence. However, probiotic supplementation improved plasma triglycerides, very-low-density lipoprotein cholesterol, insulin resistance, and plasma malondialdehyde. No RCTs included synbiotic supplementation or assessed microbiota composition. **Conclusion:** Current evidence regarding the use of probiotics and synbiotics for individuals with dementia is insufficient to support their clinical application.