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Nutrition Science



Protein

Associations of Changes in Reported and Estimated Protein and Energy Intake with Changes in Insulin Resistance, Glycated Hemoglobin, and BMI during the PREVIEW Lifestyle Intervention Study

Drummen M, Adam TC, Macdonald IA, Jalo E, Larssen TM, Martinez JA, et. al. *The American Journal of Clinical Nutrition*, 10 August 2021, doi.org/10.1093/ajcn/nqab247. [Article link](#)



Significance: Findings from the PREVIEW Study reported moderate increase in protein and decrease in energy intake during the weight-loss maintenance phase in overweight and prediabetic adults were associated with decrease in BMI and HbA1c but not with HOMA-IR (insulin resistance). The association was stronger with reported protein and energy measures compared to estimates.

Background: Observed associations of high-protein diets with changes in insulin resistance are inconclusive. Objectives: We aimed to assess associations of changes in both reported and estimated protein (PRep; PEst) and energy intake (EIRep; EIEst) with changes in HOMA-IR, glycated hemoglobin (HbA1c), and BMI (in kg/m²), in 1822 decreasing to 833 adults (week 156) with overweight and prediabetes, during the 3-y PREVIEW (PREvention of diabetes through lifestyle intervention and population studies

In Europe and around the World) study on weight-loss maintenance. Eating behavior and measurement errors (MEs) of dietary intake were assessed. Thus, observational post hoc analyses were applied. **Methods:** Associations of changes in EIEst, EIRep, PEst, and PRep with changes in HOMA-IR, HbA1c, and BMI were determined by linear mixed-model analysis in 2 arms [high-protein-low-glycemic-index (GI) diet and moderate-protein-moderate-GI diet] of the PREVIEW study. EIEst was derived from energy requirement: total energy expenditure = basal metabolic rate × physical activity level; PEst from urinary nitrogen, and urea. MEs were calculated as [(EIEst – EIRep)/EIEst] × 100% and [(PRep – PEst)/PEst] × 100%. Eating behavior was determined using the Three Factor Eating Questionnaire, examining cognitive dietary restraint, disinhibition, and hunger. **Results:** Increases in PEst and PRep and decreases in EIEst and EIRep were associated with decreases in BMI, but not independently with decreases in HOMA-IR. Increases in PEst and PRep were associated with decreases in HbA1c. PRep and EIRep showed larger changes and stronger associations than PEst and EIEst. Mean ± SD MEs of EIRep and PRep were 38% ± 9% and 14% ± 4%, respectively; ME changes in EIRep and En% PRep were positively associated with changes in BMI and cognitive dietary restraint and inversely with disinhibition and hunger. **Conclusions:** During weight-loss maintenance in adults with prediabetes, increase in protein intake and decrease in energy intake were not associated with decrease in HOMA-IR beyond associations with decrease in BMI. Increases in PEst and PRep were associated with decrease in HbA1c.

Lipids

Omega-3 Fatty Acid Dietary Supplements Consumed During Pregnancy and Lactation and Child Neurodevelopment: A Systematic Review

Nevins JEH, Donovan SM, Snetselaar L, Dewey KG, Novotny R, Stang J, et. al. *The Journal of Nutrition*, 12 August 2021. doi.org/10.1093/jn/nxab238. [Article link](#)

Significance: A systematic review to inform the Scientific Report of the 2020 Dietary Guidelines Advisory Committee found limited evidence that suggests omega-3 fatty acid supplementation during pregnancy/lactation may lead to favorable cognitive development or other outcomes in the child.



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Background: Maternal nutrition during pregnancy and lactation has profound effects on the development and lifelong health of the child. Long-chain PUFAs are particularly important for myelination and the development of vision during the perinatal period. **Objectives:** We conducted a systematic review to examine the relationship between supplementation with omega-3 fatty acids during pregnancy and/or lactation and neurodevelopment in children, to inform the Scientific Report of the 2020 Dietary Guidelines Advisory Committee. **Methods:** We identified articles on omega-3 fatty acid supplementation in pregnant and lactating women that included measures of neurodevelopment in their children (0–18 y) by searching PubMed, CENTRAL, Embase, and CINAHL Plus. After dual screening articles for inclusion, we qualitatively synthesized and graded the strength of evidence using pre-established criteria for assessing risk of bias, consistency, directness, precision, and generalizability. **Results:** We included 33 articles from 15 randomized controlled trials (RCTs) and 1 prospective cohort study. Of the 8 RCTs that delivered omega-3 fatty acid dietary supplements during pregnancy alone (200–2200 mg/d DHA and 0–1100 mg/d EPA for approximately 20 wk), 5 studies reported ≥ 1 finding that supplementation improved measures of cognitive development in the infant or child by 6%–11% ($P < 0.05$), but all 8 studies also reported ≥ 1 nonsignificant ($P > 0.05$) result. There was inconsistent or insufficient evidence for other outcomes (language, social-emotional, physical, motor, or visual development; academic performance; risks of attention deficit disorder, attention-deficit/hyperactivity disorder, autism spectrum disorder, anxiety, or depression) and for supplementation during lactation or both pregnancy and lactation. Populations with a lower socioeconomic status and adolescents were underrepresented and studies lacked racial and ethnic diversity. **Conclusions:** Limited evidence suggests that omega-3 fatty acid supplementation during pregnancy may result in favorable cognitive development in the child. There was insufficient evidence to evaluate the effects of omega-3 fatty acid supplementation during pregnancy and/or lactation on other developmental outcomes.

Carbohydrates

Rare Sugars and Their Health Effects in Humans: A Systematic Review and Narrative Synthesis of the Evidence from Human Trials

Ahmed A, Khan TA, Ramdath DD, Kendall CWC, Sievenpiper JL. *Nutrition Reviews*, 02 August 2021, doi.org/10.1093/nutrit/nuab012. [Article link](#)

Significance: A review of 50 intake studies of alternate sweeteners such as the rare sugars (including allulose, L-arabinose, D-tagatose, trehalose, and isomaltulose) reported the potential physiological and cardiometabolic benefits. However more safety and well controlled RCT studies with larger sample sizes and diverse populations are needed to substantiate these benefits. Future commercialization of these rare sugars may provide more sweetener options to help mitigate the risk associated with T2D and obesity.



This work was supported by the IAFNS [Carbohydrates Committee](#)

Context: Rare sugars are monosaccharides and disaccharides (found in small quantities in nature) that have slight differences in their chemical structure compared with traditional sugars. Little is known about their unique physiological and cardiometabolic effects in humans. **Objective:** The objective of this study was to conduct a systematic review and synthesis of controlled intervention studies of rare sugars in humans, using PRISMA guidelines. **Data sources:** MEDLINE and EMBASE were searched through October 1, 2020. Studies included both post-prandial (acute) and longer-term (≥ 1 week duration) human feeding studies that examined the effect of rare sugars (including allulose, arabinose, tagatose, trehalose, and isomaltulose) on cardiometabolic and physiological risk factors. **Data extraction:** In all, 50 studies in humans focusing on the 5 selected rare sugars were found. A narrative synthesis of the selected literature was conducted, without formal quality assessment or quantitative synthesis. **Data synthesis:** The narrative summary included the food source of each rare sugar, its effect in humans, and the possible mechanism of effect. Overall, these rare sugars were found to offer both short- and long-term benefits for glycemic control and weight loss, with effects differing between healthy individuals, overweight/obese individuals, and those with type 2 diabetes. Most studies were of small size and there was a lack of large randomized controlled trials that could confirm the beneficial effects of these rare sugars. **Conclusion:** Rare sugars could offer an opportunity for commercialization as an alternative sweetener, especially for those who are at high cardiometabolic risk.

Dietary Fructose Improves Intestinal Cell Survival and Nutrient Absorption

X Taylor SR, Ramsamooj S, Liang RJ, Katti A, Pozovskiy R, Vasan N, et. al. *Nature*, 18 August 2021. [Article link](#)

Significance: Fructose intake is linked to increase risk of obesity and cancer and an implicated pathway involves the small intestine. Mouse models have shown fructose improves intestinal cell survival, increases intestinal villus

length, and expands gut surface area. The findings may explain the increased adiposity links to Western diet, and to tumor promotion.

Fructose consumption is linked to the rising incidence of obesity and cancer, which are two of the leading causes of morbidity and mortality globally^{1,2}. Dietary fructose metabolism begins at the epithelium of the small intestine, where fructose is transported by glucose transporter type 5 (GLUT5; encoded by SLC2A5) and phosphorylated by ketohexokinase to form fructose 1-phosphate, which accumulates to high levels in the cell^{3,4}. Although this pathway has been implicated in obesity and tumour promotion, the exact mechanism that drives these pathologies in the intestine remains unclear. Here we show that dietary fructose improves the survival of intestinal cells and increases intestinal villus length in several mouse models. The increase in villus length expands the surface area of the gut and increases nutrient absorption and adiposity in mice that are fed a high-fat diet. In hypoxic intestinal cells, fructose 1-phosphate inhibits the M2 isoform of pyruvate kinase to promote cell survival^{5,6,7}. Genetic ablation of ketohexokinase or stimulation of pyruvate kinase prevents villus elongation and abolishes the nutrient absorption and tumour growth that are induced by feeding mice with high-fructose corn syrup. The ability of fructose to promote cell survival through an allosteric metabolite thus provides additional insights into the excess adiposity generated by a Western diet, and a compelling explanation for the promotion of tumour growth by high-fructose corn syrup.



Low- and No-Calorie Sweeteners

A Systematic Review of Metabolomic Biomarkers for the Intake of Sugar-Sweetened and Low-Calorie Sweetened Beverages

Muli S, Goerdten J, Oluwagbemigun K, Floegel A, Schmid M, Nöthlings U. *Metabolites*, 19 August 2021, 11(8), 546; doi.org/10.3390/metabo11080546. [Article link](#)

Significance: $^{13}\text{C}:^{12}\text{C}$ carbon isotope ratio ($\delta^{13}\text{C}$), specifically the $\delta^{13}\text{C}$ of alanine is a sensitive measure and biomarker to predict sugar sweetened beverages (SSBs) intake whereas, Acesulfame-K, saccharin, sucralose, cyclamate, and steviol glucuronide provide modest validity for predicting the short-term intake of Low-calorie beverages (LCSBs).

Intake of added sugars (AS) is challenging to assess compared with total dietary sugar because of the lack of reliable assessment methods. The reliance on self-reported dietary data in observational studies is often cited as biased, with evidence of AS intake in relation to health outcomes rated as low to moderate quality. Sugar-sweetened beverages (SSBs) are a major source of AS. A regular and high intake of SSBs is associated with an overall poor diet, weight gain, and cardiometabolic risks. An elevated intake of low-calorie sweetened beverages (LCSBs), often regarded as healthier alternatives to SSBs, is also increasingly associated with increased risk for metabolic dysfunction. In this review, we systematically collate evidence and provide perspectives on the use of metabolomics for the discovery of candidate biomarkers associated with the intake of SSBs and LCSBs. We searched the Medline, Embase, Scopus, and Web of Science databases until the end of December 2020. Seventeen articles fulfilled our inclusion criteria. We evaluated specificity and validity of the identified biomarkers following Guidelines for Biomarker of Food Intake Reviews (BFIRev). We report that the $^{13}\text{C}:^{12}\text{C}$ carbon isotope ratio ($\delta^{13}\text{C}$), particularly, the $\delta^{13}\text{C}$ of alanine is the most robust, sensitive, and specific biomarker of SSBs intake. Acesulfame-K, saccharin, sucralose, cyclamate, and steviol glucuronide showed moderate validity for predicting the short-term intake of LCSBs. More evidence is required to evaluate the validity of other panels of metabolites associated with the intake of SSBs.

Cognitive Health

Citicoline and Memory Function in Healthy Older Adults: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

Nakazaki E, Mah E, Sanoshy K, Citrolo D, Watanabe F. *The Journal of Nutrition*, Vol/ 151, Issue 8, August 2021, p2153–2160, doi.org/10.1093/jn/nxab119. [Article link](#)

Significance: Regular consumption of citicoline may be beneficial against age-related memory loss. The 12-week study in healthy older men and women with AAMI, aged 50–85 years, reported on participants who were supplemented with citicoline (a choline) that showed significant overall improvement in memory performance, specifically episodic memory, as measured by a Paired Associate test.

Background: Supplementation of citicoline (CDP-choline), a naturally occurring mononucleotide, has shown beneficial effects on memory function and behavior in populations with a wide range of impairments. However, few studies have

investigated its effect in healthy older populations. **Objective:** The objective of this study was to investigate the effects of citicoline (Cognizin®), on memory in healthy elderly populations with age-associated memory impairment (AAMI). **Methods:** A total of 100 healthy men and women aged between 50 and 85 y with AAMI participated in this randomized, double-blind, placebo-controlled trial. Participants were randomized to receive placebo (n = 51) or citicoline (n = 49; 500 mg/d) for 12 wk. Memory function was assessed at baseline and end of the intervention (12 wk) using computerized tests (Cambridge Brain Sciences, Ontario, Canada). Safety measurements included adverse events query, body weight, blood pressure, and hematology and metabolic panel. Intent-to-treat analysis was conducted using ANCOVA for the primary and secondary outcome variables with Bonferroni correction for multiple comparisons. **Results:** A total of 99 out of 100 participants completed the study in its entirety. After the 12-wk intervention, participants supplemented with citicoline showed significantly greater improvements in secondary outcomes of episodic memory (assessed by the Paired Associate test), compared with those on placebo (mean: 0.15 vs. 0.06, respectively, P = 0.0025). Composite memory (secondary outcome), calculated using the scores of 4 memory tests, also significantly improved to a greater extent following citicoline supplementation (mean: 3.78) compared with placebo (mean: 0.72, P = 0.0052). **Conclusions:** Dietary supplementation of citicoline for 12 wk improved overall memory performance, especially episodic memory, in healthy older males and females with AAMI. The findings suggest that regular consumption of citicoline may be safe and potentially beneficial against memory loss due to aging.

Sodium

Effect of Salt Substitution on Cardiovascular Events and Death

Neal B, Wu Y, Feng X, Zhang R, Zhang Y, Shi J, et. al. *N Engl J Med.* 2021 Aug 29. doi: 10.1056/NEJMoa2105675. [Article link](#)

Significance: Over a 4-year period, researchers tracked 20,000 older adults from 600 villages in China. The study of subjects with a history of stroke – or who were 60 years or older and had high blood pressure – showed a significant decline in the rates of stroke, major cardiovascular events, and all-cause mortality in the KCl substituted group compared to the NaCl control.

Background: Salt substitutes with reduced sodium levels and increased potassium levels have been shown to lower blood pressure, but their effects on cardiovascular and safety outcomes are uncertain. **Methods:** We conducted an open-label, cluster-randomized trial involving persons from 600 villages in rural China. The participants had a history of stroke or were 60 years of age or older and had high blood pressure. The villages were randomly assigned in a 1:1 ratio to the intervention group, in which the participants used a salt substitute (75% sodium chloride and 25% potassium chloride by mass), or to the control group, in which the participants continued to use regular salt (100% sodium chloride). The primary outcome was stroke, the secondary outcomes were major adverse cardiovascular events and death from any cause, and the safety outcome was clinical hyperkalemia. **Results:** A total of 20,995 persons were enrolled in the trial. The mean age of the participants was 65.4 years, and 49.5% were female, 72.6% had a history of stroke, and 88.4% a history of hypertension. The mean duration of follow-up was 4.74 years. The rate of stroke was lower with the salt substitute than with regular salt (29.14 events vs. 33.65 events per 1000 person-years; rate ratio, 0.86; 95% confidence interval [CI], 0.77 to 0.96; P = 0.006), as were the rates of major cardiovascular events (49.09 events vs. 56.29 events per 1000 person-years; rate ratio, 0.87; 95% CI, 0.80 to 0.94; P < 0.001) and death (39.28 events vs. 44.61 events per 1000 person-years; rate ratio, 0.88; 95% CI, 0.82 to 0.95; P < 0.001). The rate of serious adverse events attributed to hyperkalemia was not significantly higher with the salt substitute than with regular salt (3.35 events vs. 3.30 events per 1000 person-years; rate ratio, 1.04; 95% CI, 0.80 to 1.37; P = 0.76). **Conclusions:** Among persons who had a history of stroke or were 60 years of age or older and had high blood pressure, the rates of stroke, major cardiovascular events, and death from any cause were lower with the salt substitute than with regular salt.

Gut Microbiome

Luminal Bioavailability of Orally Administered ω -3 PUFAs in the Distal Small Intestine, and Associated Changes to the Ileal Microbiome, in Humans with a Temporary Ileostomy

Y Nana G, Mitra S, Watson H, Young C, Wood HW, Perry SL, et. al. *The Journal of Nutrition*, Vol/ 151, Issue 8, August 2021, p2142–2152, doi.org/10.1093/jn/nxab113. [Article link](#)

Significance: Oral ingestion of ω -3 PUFAs over 28 weeks in older adults leads to an increase in ileal ω -3 PUFA levels. This is correlated with higher abundance of Bacteroides and reduced abundance of other genera, including Actinomyces in individuals with temporary ileostomy.

Background: Oral administration of purified omega-3 (ω -3) PUFAs is associated with changes to the fecal microbiome. However, it is not known whether this effect is associated with increased PUFA concentrations in the gut. **Objectives:** We investigated the luminal bioavailability of oral ω -3 PUFAs (daily dose 1 g EPA and 1g DHA free fatty acid equivalents as triglycerides in soft-gel capsules, twice daily) and changes to the gut microbiome, in the ileum. **Methods:** Ileostomy fluid (IF) and blood were obtained at baseline, after first capsule dosing (median 2 h), and at a similar time after final dosing on day 28, in 11 individuals (median age 63 y) with a temporary ileostomy. Fatty acids were measured by LC–tandem MS. The ileal microbiome was characterized by 16S rRNA PCR and Illumina sequencing. **Results:** There was a mean 6.0 ± 9.8 -fold and 6.6 ± 9.6 -fold increase in ileal EPA and DHA concentrations (primary outcome), respectively, at 28 d, which was associated with increased RBC ω -3 PUFA content ($P \leq 0.05$). The first oral dose did not increase the ileal ω -3 PUFA concentration except in 4 individuals, who displayed high luminal EPA and DHA concentrations, which reduced to concentrations similar to the overall study population at day 28, suggesting physiological adaptation. Bacteroides, Clostridium, and Streptococcus were abundant bacterial genera in the ileum. Ileal microbiome variability over time and between individuals was large, with no consistent change associated with acute ω -3 PUFA dosing. However, high concentrations of EPA and DHA in IF on day 28 were associated with higher abundance of Bacteroides ($r_2 > 0.86$, $P < 0.05$) and reduced abundance of other genera, including Actinomyces ($r_2 > 0.94$, $P < 0.05$). **Conclusions:** Oral administration of ω -3 PUFAs leads to increased luminal ω -3 PUFA concentrations and changes to the microbiome, in the ileum of individuals with a temporary ileostomy.