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Nutrition Briefs



Dietary Patterns

Mediterranean Diet Adherence is Associated with Lower Dementia Risk, Independent of Genetic Predisposition: Findings from the UK Biobank Prospective Cohort Study

Oliver M. Shannon, Janice M. Ranson, Sarah Gregory, Helen Macpherson, Catherine Shannon et al. *BMC Medicine* (2023) 21:81 doi.org/10.1186/s12916-023-02772-3. Article link

Significance: Higher adherence to a Mediterranean Diet was linked to lower dementia risk that was independent of genetic risk, signaling the important role of diet in potentially preventing dementia.

Background: The identification of effective dementia prevention strategies is a major public health priority, due to the enormous and growing societal cost of this condition. Consumption of a Mediterranean diet (MedDiet) has been proposed to reduce dementia risk. However, current evidence is inconclusive and is typically derived from small cohorts with limited dementia cases. Additionally, few studies have explored the interaction between diet and genetic risk of dementia. **Methods**: We used Cox proportional hazard regression models to explore the associations between MedDiet adherence, defined using two different scores (Mediterranean Diet Adherence Screener [MEDAS] continuous and Mediterranean diet Pyramid [PYRAMID] scores), and incident all-cause dementia risk in 60,298 participants from UK Biobank, followed for an average 9.1 years. The interaction between diet and polygenic risk for dementia was also tested. **Results:** Higher MedDiet adherence was associated with lower dementia risk (MEDAS continuous: HR = 0.77, 95% CI = 0.65 - 0.91; PYRAMID: HR = 0.86, 95% CI = 0.73 - 1.02 for highest versus lowest tertiles). There was no significant interaction between MedDiet adherence defined by the MEDAS continuous and PYRAMID scores and polygenic risk for dementia. **Conclusions:** Higher adherence to a MedDiet was associated with lower dementia risk, independent of genetic risk, underlining the importance of diet in dementia prevention interventions.

Carbohydrates

Low-Carbohydrate Diet Scores and Mortality Among Adults With Incident Type 2 Diabetes

Yang Hu, Gang Liu, Edward Yu, Biqi Wang, Clemens Wittenbecher, JoAnn E. Manson, Eric B. Rimm, et. al. *Diabetes Care*. Feb 14, 2023.doi.org/10.2337/dc22-2310. **Article link**



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Objective: The current study aims to prospectively examine the association between postdiagnosis lowcarbohydrate diet (LCD) patterns and mortality among individuals with type 2 diabetes (T2D). Research designs and methods: Among participants with incident diabetes identified in the Nurses' Health Study and Health Professionals Follow-up Study, an overall total LCD score (TLCDS) was calculated based on the percentage of energy as total carbohydrates. In addition, vegetable (VLCDS), animal (ALCDS), healthy (HLCDS), and unhealthy LCDS (ULCDS) were further derived that emphasized different sources and quality of macronutrients. Multivariable-adjusted Cox models were used to assess the association between the LCDS and mortality. Results: Among 10,101 incident T2D cases contributing 139,407 person-years during follow-up, we documented 4,595 deaths of which 1,389 cases were attributed to cardiovascular disease (CVD) and 881 to cancer. The pooled multivariable-adjusted hazard ratios (HRs, 95% CIs) of total mortality per 10-point increment of postdiagnosis LCDS were 0.87 (0.82, 0.92) for TLCDS, 0.76 (0.71, 0.82) for VLCDS, and 0.78 (0.73, 0.84) for HLCDS. Both VLCDS and HLCDS were also associated with significantly lower CVD and cancer mortality. Each 10-point increase of TLCDS, VLCDS, and HLCDS from prediagnosis to postdiagnosis period was associated with 12% (7%, 17%), 25% (19%, 30%), and 25% (19%, 30%) lower total mortality, respectively. No significant associations were observed for ALCDS and ULCDS. Conclusions: Among people with T2D, greater adherence to LCD patterns that emphasize high-quality sources of macronutrients was significantly associated with lower total, cardiovascular, and cancer mortality.

The Relationship Between Major Food Sources of Fructose and Cardiovascular Outcomes: A Systematic Review and Dose-Response Meta-Analysis of Prospective Studies

Tingting Sun, Yabing Zhang, Lin Ding, Yonggang Zhang, Tao Li, Qian Li. **Adv Nutr.** 2023 Mar;14(2):256-269. doi: 10.1016/j.advnut.2022.12.002. **Article link**

Significance: The impact of fructose on CVD outcomes is influenced by food sources. Comparing fructose from multiple food sources, an adverse association was found only between fructose from sugar-sweetened beverages (SSB) and CVD, CHD, and stroke morbidity and mortality.

There is emerging evidence of associations between intake of sugar-sweetened beverages (SSBs), those that include various forms of added sugar, and increased risk of cardiovascular disease (CVD) but whether consumption of other dietary sources of fructose affects CVD is unclear. In this study, we conducted a meta-analysis to examine potential dose-response relationships between such foods and CVD, coronary heart disease (CHD), and stroke morbidity and mortality. We systematically searched the literature indexed in PubMed. Embase, and the Cochrane Library from the inception of each database to February 10, 2022. We included prospective cohort studies analyzing the association between at least 1 dietary source of fructose and CVD, CHD, and stroke. Based on data from 64 included studies, summary HRs and 95% CIs were calculated for the highest intake category compared with the lowest, and dose-response analyses were performed. Of all fructose sources examined, only SSB intakes showed positive associations with CVD, giving summary HRs per 250 mL/d increase of 1.10 (95% CI: 1.02, 1.17) for CVD, 1.11 (95% CI: 1.05, 1.17) for CHD, 1.08 (95% CI: 1.02, 1.13) for stroke morbidity, and 1.06 (95% CI: 1.02, 1.10) for CVD mortality. Conversely, 3 dietary sources showed protective associations: between fruits and CVD morbidity (HR: 0.97; 95% CI: 0.96, 0.98), fruits and CVD mortality (HR: 0.94; 95% CI: 0.92, 0.97), yogurt and CVD mortality (HR: 0.96; 95% CI: 0.93, 0.99), and breakfast cereals and CVD mortality (HR: 0.80; 95% CI: 0.70, 0.90). All these relationships were linear except for fruit, which was J-shaped: CVD morbidity was the lowest at 200 g/d and there was no protective association above 400 g/d. These findings indicate that the adverse associations between SSBs and CVD, CHD, and stroke morbidity and mortality do not extend to other dietary sources of fructose. The food matrix seemed to modify the association between fructose and cardiovascular outcomes.

Protein

Effects of Whey and Soy Protein Supplementation on Inflammatory Cytokines in Older Adults: A Systematic Review and Meta-Analysis

Konstantinos Prokopidis, Mohsen Mazidi, Rajiv Sankaranarayanan, Behnam Tajik, Anne McArdle, Masoud Isanejad. *Br J Nutr.* 2023 Mar 14;129(5):759-770. doi: 10.1017/S0007114522001787. Article link

Significance: A systematic review including 31 randomized control studies found whey and soy protein

supplementation facilitated anti-inflammatory effects by reducing circulating IL-6 and TNF- α levels. This effect may be further enhanced by soy isoflavones, and in individuals with sarcopenia.

Background and Aims: Low-grade inflammation is a mediator of muscle proteostasis. This study aimed to investigate the effects of isolated whey and soy proteins on inflammatory markers. Methods: We conducted a systematic literature search of randomized controlled trials (RCT) through MEDLINE, Web of Science, Scopus, and Cochrane Library databases from inception until September 2021. To determine the effectiveness of isolated proteins on circulating levels of C-reactive protein (CRP), IL-6 and TNF- α , a meta-analysis using a random-effects model was used to calculate the pooled effects (CRD42021252603). Results: Thirty-one RCT met the inclusion criteria and were included in the systematic review and meta-analysis. A significant reduction of circulating IL-6 levels following whey protein [Mean Difference (MD): -0.79, 95 % CI: -1.15, -0.42, I2 = 96 %] and TNF- α levels following soy protein supplementation (MD: -0.16, 95 % CI: -0.26, -0.05, I2 = 68 %) was observed. The addition of soy isoflavones exerted a further decline in circulating TNF- α levels (MD: -0.20, 95 % CI: -0.31, -0.08, I2 = 34 %). According to subgroup analysis, whey protein led to a statistically significant decrease in circulating IL-6 levels in individuals with sarcopenia and pre-frailty (MD: -0.98, 95% CI: -1.56, -0.39, I2 = 0%). These findings may be dependent on participant characteristics and treatment duration. Conclusions: These data support that whey and soy protein supplementation elicit anti-inflammatory effects by reducing circulating IL-6 and TNF- α levels, respectively. This effect may be enhanced by soy isoflavones and may be more prominent in individuals with sarcopenia.

Low- and No-Calorie Sweeteners

The Dietary Sweetener Sucralose is a Negative Modulator of T Cell-Mediated Responses

Fabio Zani, Julianna Blagih, Tim Gruber, Michael D. Buck, Nicholas Jones, Marc Hennequart, Clare L. Newell, et. al. *Nature* volume 615, pages705–711 (2023). Article link

Significance: A study in mice suggests that a high intake of sucralose can limit T cell-mediated responses. This immunomodulatory effect could be used in therapy to mitigate T cell-dependent autoimmune disorders pending further studies.

Artificial sweeteners are used as calorie-free sugar substitutes in many food products and their consumption has increased substantially over the past years1. Although generally regarded as safe, some concerns have been raised about the long-term safety of the consumption of certain sweeteners2,3,4,5. In this study, we show that the intake of high doses of sucralose in mice results in immunomodulatory effects by limiting T cell proliferation and T cell differentiation. Mechanistically, sucralose affects the membrane order of T cells, accompanied by a reduced efficiency of T cell receptor signaling and intracellular calcium mobilization. Mice given sucralose show decreased CD8+ T cell antigen-specific responses in subcutaneous cancer models and bacterial infection models, and reduced T cell function in models of T cell-mediated autoimmunity. Overall, these findings suggest that a high intake of sucralose can dampen T cell-mediated responses, an effect that could be used in therapy to mitigate T cell-dependent autoimmune disorders.

Cognitive Health

Integrating Nutrient Biomarkers, Cognitive Function, and Structural MRI Data to Build Multivariate Phenotypes of Healthy Aging

Tanveer Talukdar, Christopher E Zwilling, Aron K Barbey. *J Nutr*. 2023 Mar 23;S0022-3166(23)35485-3. doi: 10.1016/j.tjnut.2023.03.016. **Article link**

Significance: Converging innovations in nutritional epidemiology, cognitive neuroscience, brain imaging and data fusion have enabled a novel interdisciplinary approach to nutrition, cognition and brain health.

Background: Research in the emerging field of Nutritional Cognitive Neuroscience demonstrates that many aspects of nutrition - from entire diets to specific nutrients - affect cognitive performance and brain health. **Objective**: While prior research has primarily examined the bivariate relationship between nutrition and cognition, or nutrition and brain health, the present study sought to investigate the joint relationship between these essential and interactive elements of human health. **Methods:** We applied a state-of-the-art data fusion method, Coupled Matrix Tensor Factorization, to characterize the joint association between measures of nutrition (52 nutrient biomarkers), cognition (Wechsler Abbreviated Test of Intelligence and Wechsler Memory Scale), and brain health (high-resolution Magnetic Resonance Imaging measures of structural brain volume) within a

cross-sectional sample of 111 healthy older adults that had an average age of 69.1 years, were 62% female and had an average Body Mass Index of 26.0. **Results**: Data fusion uncovered 3 latent factors that capture the joint association between specific nutrient profiles, cognitive measures, and cortical volumes, demonstrating the respects in which these health domains are coupled. Hierarchical cluster analysis further revealed systematic differences between the observed latent factors, providing evidence for multivariate phenotypes that represent high versus low levels of performance across multiple health domains. The primary features that distinguish between each phenotype were: (i) nutrient biomarkers for monounsaturated and polyunsaturated fatty acids; (ii) cognitive measures of immediate, auditory, and delayed memory; and (iii) brain volumes within frontal, temporal, and parietal cortex. **Conclusions**: By incorporating innovations in nutritional epidemiology (nutrient biomarker analysis), cognitive neuroscience (high-resolution structural brain imaging), and statistics (data fusion), the present study provides an interdisciplinary synthesis of methods that elucidate how nutrition, cognition, and brain health are integrated through lifestyle choices that affect healthy aging.

Perspective: Advancing Dietary Guidance for Cognitive Health - Focus on Solutions to Harmonization of Test Selection, Implementation and Evaluation

Amy R Romijn, Hayley Young, Marie E Latulippe, Linda Snetselaar, Peter Willatts, Lysanne Melanson, Richard Gershon, Christy Tangney. *Adv Nutr*. 2023 Mar 28;S2161-8313(23)00279-X. doi: 10.1016/j.advnut.2023.03.010. Article link

Significance: A review of cognitive tasks in nutrition research, with a focus on solutions towards informing dietary guidance for cognitive health.

This paper was supported by **IAFNS Cognitive Health Committee.**

This perspective paper is a product of a workshop of experts convened by Institute for the Advancement of Food and Nutrition Sciences (IAFNS), a non-profit organization that brings together scientists from government, academia, and industry to catalyze science relevant to food and nutrition. An expert group was convened in March 2022 to discuss the current issues surrounding cognitive task selection in nutrition research, with a focus on solutions towards informing dietary guidance for cognitive health, to address a gap identified in the 2020 US DGAC report, specifically the "considerable variation in testing methods used, [and] inconsistent validity and reliability of cognitive testing methods" (p.31). To address this issue, we firstly undertook an umbrella review of relevant reviews already undertaken; these indicate agreement on some of the issues that affect heterogeneity in task selection, and on many of the fundamental principles underlying selection of cognitive outcome measures. However, resolving the points of disagreement is critical to ensuring meaningful impact on the issue of heterogeneity in task selection; these issues hamper evaluation of existing data for informing dietary guidance. This summary of the literature is therefore followed by the expert group's perspective in the form of a discussion of potential solutions to these challenges, with the aim of building on the work of previous reviews in the area and advancing dietary guidance for cognitive health. STATEMENT OF SIGNIFICANCE: Despite several high-quality reviews in this field over the last two decades, there has been little in the way of substantive change in the methods being used to conduct studies, hampering harmonization of the evidence and thus, its utility for informing dietary guidance. The present paper comprehensively updates the field by firstly providing an umbrella review of the published reviews, followed by the IAFNS expert group's perspective on how to move the field forward by addressing the challenges and areas of disagreement in the existing reviews.

Lipids

The Metabolizable Energy and Lipid Bioaccessibility of Tree Nuts and Peanuts: A Systematic Review with Narrative Synthesis of Human and in vitro Studies

Cassandra J Nikodijevic, Yasmine C Probst, Sze-Yen Tan, Elizabeth P Neale. *Adv Nutr*. 2023 Mar 17;S2161-8313(23)00275-2. doi: 10.1016/j.advnut.2023.03.006. Article link

Significance: Regular intake of energy-dense nuts has not been associated with weight gain. A recent systematic review suggests that lower encapsulated lipid release from cell wall during processing (including heat and physical treatment) and digestion, may explain the lower available metabolizable energy in peanuts and tree nuts.

Nuts are an energy-dense food, yet regular consumption is not associated with weight gain. A proportion of the fats found within nuts remains encapsulated within cell walls and cannot be digested. Metabolizable energy can be explored by measuring fecal fat excretion in human studies, and fat release among in vitro studies. This systematic review with

with narrative synthesis aimed to examine the metabolizable energy of tree nuts and peanuts (PROSPERO CRD42021252287). PubMed, MEDLINE, CINAHL, Cochrane, and Embase databases were searched to June 2021. Both in vitro and human studies (adults ≥18 years) were included. Data was synthesized via narrative synthesis with results reported in summary tables and compared between form, processing, and dose of nuts, where available. Twenty-one studies were included. The metabolizable energy of nuts was consistently lower than that predicted by Atwater factors for investigated nut types (almonds, cashews, hazelnuts, pistachios, walnuts, and peanuts). The mechanisms may relate to a lower fat release from nuts, hence higher fecal fat excretion; however, this review did not consider the digestibility of carbohydrates and protein which should be considered when interpreting the outcomes. Metabolizable energy (ME) was influenced by nut type (ME = 22.6kJ/g for pistachios; ME = 18.5 kJ/g for raw almonds), physical form (flour > chopped > whole nuts), heat processing (butter > roasted > raw) and dose of consumption. The lower-than-expected metabolizable energy may explain a lack of association between nut intake and body weight observed in the literature and has implications for the development of food composition databases, food labelling and informing dietary guidelines. However, the strength of the evidence base was reduced by the variation in methods used between studies, suggesting that further clinical trials are needed to determine the impact of the findings of this review for clinical dietetics. STATEMENT OF SIGNIFI-CANCE: This study is the first to systematically review the metabolizable energy content and lipid bio accessibility of tree nuts and peanuts. The results of this study suggest that the metabolizable energy of nuts is lower than expected, due to a lower lipid release during processing and digestion, and is impacted by nut type, physical processing, and heat treatment of nuts.

Sodium

Characterizing the Effect of Sodium Reduction and Monosodium Glutamate Supplementation on White and Multigrain Breads

Aubrey N Dunteman, Soo-Yeun Lee. *J Food Sci*. 2023 Mar;88(3):1128-1143. doi: 10.1111/1750-3841.16460. **Article link**

Significance: A study on salt reduction (43% or 60%) in white and multigrain bread products found that the addition of MSG as a flavor enhancer mitigated loss in consumer liking scores by improving on key drivers such as texture, saltiness and aftertaste.

Sodium overconsumption has become a serious health concern resulting in the Food and Drug Administration (FDA) publishing voluntary sodium reduction guidelines for a wide spectrum of packaged and processed foods. Reducing sodium through the removal of salt may decrease the palatability of foods, thus increasing the need for new approaches to prevent such palatability loss. The objective of this research was to characterize white and multigrain breads with either 43% or 60% reduction in sodium and with and without monosodium glutamate (MSG) using descriptive analysis methodology as well as to identify the drivers of liking for white and multigrain breads of varying sodium contents with and without MSG. Significant differences were identified in the attributes of salty taste and aftertaste, savory aftertaste, and chewy and firm textures in white bread and of salty taste and aftertaste, sweet taste, and density in multigrain bread. By regressing consumer test data of these breads onto their principal component analysis biplots, textural attributes and salty taste and aftertaste were identified as primary drivers of liking in white and multigrain breads. Flavor enhancers such as MSG show promise in mitigating palatability loss that occurs when the sodium content of bread is reduced and thus provide a promising solution to produce breads with an improved nutritional profile. Future research on flavor enhancement in other food matrices would be valuable as well as in other bread and carbohydrate-based food categories. PRACTICAL APPLICATION: The findings of our study suggest that texture and a salty taste and aftertaste drive consumer liking of reduced-sodium white and multigrain breads and liking of breads could be improved with the addition of monosodium glutamate. Increasing the acceptance of reduced-sodium food products could help to improve the health of the American population by resulting in a reduced risk of hypertension and subsequently heart attacks and stroke.

Gut Microbiome

Carotenoids and Their Health Benefits as Derived via Their Interactions with Gut Microbiota

Abdulkerim Eroglu, Ibrahim S Al'Abri, Rachel E Kopec, Nathan Crook, Torsten Bohn. *Adv Nutr.* 2023 Mar;14(2):238-255. doi: 10.1016/j.advnut.2022.10.007. Article link

Significance: This study discussed the beneficial role carotenoids played in gut health including effects on IgA

stimulation and tight junctions' stabilization involved in mucosal and gut barriers. Research gaps in carotenoidgut microbiota interactions were also identified.

Carotenoids have been related to a number of health benefits. Their dietary intake and circulating levels have been associated with a reduced incidence of obesity, diabetes, certain types of cancer, and even lower total mortality. Their potential interaction with the gut microbiota (GM) has been generally overlooked but may be of relevance, as carotenoids largely bypass absorption in the small intestine and are passed on to the colon, where they appear to be in part degraded into unknown metabolites. These may include apo-carotenoids that may have biological effects because of higher aqueous solubility and higher electrophilicity that could better target transcription factors, i.e., NF-κB, PPARγ, and RAR/RXRs. If absorbed in the colon, they could have both local and systemic effects. Certain microbes that may be supplemented were also reported to produce carotenoids in the colon. Although some bactericidal aspects of carotenoids have been shown in vitro, a few studies have also demonstrated a prebiotic-like effect, resulting in bacterial shifts with health-associated properties. Also, stimulation of IgA could play a role in this respect. Carotenoids may further contribute to mucosal and gut barrier health, such as stabilizing tight junctions. This review highlights potential gut-related health-beneficial effects of carotenoids and emphasizes the current research gaps regarding carotenoid-GM interactions.

Emerging Science: Nutrition

Emerging Science Category: Vitamin D Supplementation and Fractures

The Effect of Monthly Vitamin D Supplementation on Fractures: A Tertiary Outcome from the Population-Based, Double-Blind, Randomized, Placebo-Controlled D-Health Trial

Mary Waterhouse, Peter R Ebeling, Donald S A McLeod, Dallas English, Briony Duarte Romero, Catherine Baxter, et al. *Lancet Diabetes and Endocrinology*. March 31, 2023. doi.org/10.1016/S2213-8587(23)00063-3. Article link

Significance: A five-year population-based, double-blind, randomized, placebo-controlled trial of oral vitamin D3 supplementation in older Australian adults found that bolus doses of vitamin D administered monthly (60,000IU) did not increase fracture risk. Long-term studies on impact of oral D3 supplementation for reducing total fractures in older adults are needed.

Summary: Low serum 25-hydroxy vitamin D concentration is associated with increased fracture risk. It is uncertain whether vitamin D supplementation reduces fractures, or whether intermittent doses are harmful. We aimed to investigate if supplementing adults living in Australia with monthly doses of 60 000 international units (IU) vitamin D₃ for 5 years or less altered the rate of fractures. **Methods:** We did a population-based, doubleblind, randomized, placebo-controlled trial of oral vitamin D3 supplementation (60 000 IU per month) for up to 5 years in adults aged 60–84 years living in Australia. We randomly assigned (1:1) 21 315 participants to either vitamin D or placebo. We ascertained fractures through linkage with administrative datasets. The main outcome was total fractures. Additional outcomes were non-vertebral, major osteoporotic (hip, wrist, proximal humerus, and spine), and hip fractures. We excluded participants (989 [4.6%]) without linked data, and estimated hazard ratios (HRs) and 95% CIs using flexible parametric survival models. The trial is registered with the Australian New Zealand Clinical Trials Registry, ACTRN12613000743763, and the trial intervention ended in February 2020. Findings: Between Feb 14, 2014, and June 17, 2015, we recruited 21 315 participants. For the current analysis, we included 20 326 participants (vitamin D 10 154 [50.0%]; placebo 10 172 [50.0%]). 9295 (45.7%) of 20 326 participants were women and the mean age was 69.3 years (SD 5.5). Over a median follow-up of 5.1 years (IQR $5\cdot 1-5\cdot 1$, 568 ($5\cdot 6\%$) participants in the vitamin D group and 603 ($5\cdot 9\%$) in the placebo group had one or more fractures. There was no effect on fracture risk overall (HR 0.94 [95% CI 0.84–1.06]), and the interaction between randomization group and time was not significant (p=0.14). However, the HR for total fractures appeared to decrease with increasing follow-up time. The overall HRs for non-vertebral, major osteoporotic, and hip fractures were 0.96 (95% CI 0.85–1.08), 1.00 (0.85–1.18), and 1.11 (0.86–1.45), respectively. Interpretation: These findings do not support concerns that bolus doses of vitamin D administered monthly increase fracture risk. Longterm supplementation might reduce the incidence of total fractures, but additional research is needed to clarify this effect

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