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## Dietary Patterns

### Dietary Patterns and Health: Insights from NESR Systematic Reviews to Inform the Dietary Guidelines for Americans

Laural K English, Ramkripa Raghavan, Julie E Obbagy, Emily H Callahan, Amanda K Fultz, Julie E H Nevins, Sara Scinto-Madonich, et. al. *J Nutr Educ Behav.* 2024 Jan;56(1):75-87. doi: 10.1016/j.jneb.2023.10.001. [Article link](#)

**Significance:** This article provides current Agriculture Department perspectives on conducting systematic reviews. The relationship between dietary patterns and health and approaches to dietary guidance across life stages address gaps in dietary pattern research..

This perspective article shares unique insights from the extensive experience of the US Department of Agriculture Nutrition Evidence Systematic Review branch in conducting systematic reviews on dietary patterns and health outcomes to inform the Dietary Guidelines for Americans. Methodological approaches for reviewing dietary patterns research are described, including approaches to operationalizing definitions and analyzing labeled dietary patterns. The review also describes techniques for synthesizing dietary patterns research across life stages in systematic reviews that inform food-based, federal dietary guidance. Current research activities and recommendations for how to improve or address gaps in dietary patterns research in the future are also discussed.

## Carbohydrates

### Ultra-Processed Foods and Human Health: A Systematic Review and Meta-Analysis of Prospective Cohort Studies

Marilena Vitale, Giuseppina Costabile, Roberta Testa, Giovanna D'Abbronzio, Immacolata Cristina Nettore, Paolo Emidio Macchia, Rosalba Giacco. *Adv Nutr.* 2024 Jan;15(1):100121. doi:10.1016/j.advnut.2023.09.009. [Article link](#)

**Significance:** Level of risks associated with UPF intake and risks of diabetes, hypertension, hyperlipidemia, and obesity varied significantly between methods used for assessing UPF consumption. Future studies on UPFs and disease risks need to consider methodological differences when interpreting and extrapolating results.

Evidence of associations between ultra-processed foods (UPF) and increased risk of cardiovascular disease is emerging, but it is unclear how much this is influenced by the methodology used to assess the UPF intake or by the level of consumption. We conducted a meta-analysis to evaluate 1) the association between UPF consumption and risk of diabetes, hypertension, dyslipidemia, and obesity, using prospective cohort studies; 2) the differential associations depending on the methodology used to assess UPF intake and the level of UPF consumption and 3) the quality of evidence using the NutriGrade scoring system. A systematic literature search was conducted in PubMed/MEDLINE, ISI Web of Science, and Scopus through 1 April 2023, on studies conducted in humans providing data for the highest compared with the lowest UPF consumption categories. Summary relative ratios (RRs) and 95% confidence intervals (95% CI) were estimated using a random-effects model. Out of 4522 articles retrieved from the literature search, 25 reports met the criteria for inclusion in the meta-analysis, 7 for diabetes, 5 for hypertension, 3 for dyslipidemia, and 13 for obesity. A consistently positive association between high UPF intake and increased risk of developing diabetes (37%), hypertension (32%), hypertriglyceridemia (47%), low HDL cholesterol concentration (43%), and obesity (32%) was observed, even if the quality of evidence was not satisfying. However, these risks varied significantly depending on the methodology used to assess UPF consumption, with a difference of more than 50% between the methods. Based on the level of intake, we did not observe significant differences in the results. These findings show that UPF consumption is associated with higher risk of diabetes, hypertension, dyslipidemia, and obesity, but the level of risk consistently changes depending on the methodology used to assess UPF intake. Therefore, caution should be used when interpreting and extrapolating the results.

## Protein

### Protein Hydrolysates and Bioactive Peptides as Mediators of Blood Glucose-A Systematic Review and Meta-Analysis of Acute and Long-Term Studies

Arig Elbira, Maryam Hafiz, Alan Javier Hernández-Álvarez, Michael A Zulyniak, Christine Boesch. *Nutrients.* 2024 Jan 22;16(2):323. doi: 10.3390/nu16020323. [Article link](#)

**Significance:** Protein hydrolysates significantly improved glycemic response in adults and may help in managing future risk of diabetes onset.

Type 2 diabetes mellitus (T2DM) is a major public health concern associated with high mortality and reduced life expectancy. Since diabetes is closely linked with lifestyle, not surprisingly, nutritional intervention and increased physical activity could play a vital role in attenuating the problems related to

diabetes. Protein hydrolysates (PHs) and their bioactive peptides (BP) have been shown to exert a wide range of biological effects, including antioxidative, antihypertensive, and particularly hypoglycaemic activities. To better understand the efficacy of such interventions, a systematic review and meta-analysis of randomised controlled trials (RCTs) were performed concerning the influence of protein hydrolysates on glycaemic biomarkers in subjects with and without hyperglycaemia. Five different databases were used to search for RCTs. In total, 37 RCTs were included in the systematic review and 29 RCTs in the meta-analysis. The meta-analysis revealed a significant reduction in postprandial blood glucose response (PPGR) in normoglycaemic (-0.22 mmol/L; 95% CI -0.43, -0.01;  $p \leq 0.05$ ) and in hyperglycaemic adults (-0.88 mmol/L; 95% CI -1.37, -0.39;  $p \leq 0.001$ ) compared with the respective control groups. A meta-regression analysis revealed a dose-dependent response for PPGR following PH consumption in normoglycaemic adults, specifically for doses  $\leq 30$  g. The postprandial blood insulin responses (PPIR) were significantly higher after the ingestion of PHs in both the group with and the group without hyperglycaemia, respectively (23.05 mIU/L; 95% CI 7.53, 38.57;  $p \leq 0.01$  and 12.57 mIU/L; 95% CI 2.72, 22.41;  $p \leq 0.01$ ), compared with controls. In terms of long-term responses, there was a small but significant reduction in both fasting blood glucose (FBG) and fasting glycated haemoglobin (HbA1c) in response to PH compared with the control group ( $p < 0.05$ ). The PHs significantly improved the parameters of glycaemia in adults and, hence, it may contribute to the management and regulation of the future risk of developing T2DM.

## Low- and No-Calorie Sweeteners

### Effect of Low- and No-Calorie Sweeteners on the Gut Microbiota: A Review of Clinical Trials and Cross-Sectional Studies

Ellie Gauthier, Fermin I Milagro, Santiago Navas-Carretero. *Nutrition*. 2024 Jan;117:112237. doi: 10.1016/j.nut.2023.112237. [Article link](#)

**Significance:** Gut microbial response to sweetener intake could be mediated by microbial composition at baseline. Future approaches using personalized microbial response to low- and no-calorie sweeteners, longer intervention protocols, larger cohorts and practical sweetener dosage are warranted.

Use of non-nutritive sweeteners (NNSs) has increased worldwide in recent decades. However, evidence from preclinical studies shows that sweetener consumption may induce glucose intolerance through changes in the gut microbiota, which raises public health concerns. As studies conducted on humans are lacking, the aim of this review was to gather and summarize the current evidence on the effects of NNSs on human gut microbiota. Only clinical trials and cross-sectional studies were included in the review. Regarding NNSs (i.e. saccharin, sucralose, aspartame, and stevia), only two of five clinical trials showed significant changes in gut microbiota composition after the intervention protocol. These studies concluded that saccharin and sucralose impair glycemic tolerance. In three of the four cross-sectional studies an association between NNSs and the microbial composition was observed. All three clinical trials on polyols (i.e. xylitol) showed prebiotic effects on gut microbiota, but these studies had multiple limitations (publication date, dosage, duration) that jeopardized their validity. The microbial response to NNSs consumption could be strongly mediated by the gut microbial composition at baseline. Further studies in which the potential personalized microbial response to NNSs consumption is acknowledged, and that include longer intervention protocols, larger cohorts, and more realistic sweetener dosage are needed to broaden these findings.

## Cognitive Health

### Current Understanding of the Alzheimer's Disease-Associated Microbiome and Therapeutic Strategies

Dong-Oh Seo, David M Holtzman. *Exp Mol Med*. 2024 Epub Jan. 4;56(1):86-94. doi: 10.1038/s12276-023-01146-2. [Article link](#)

**Significance:** This review summarized current evidence on the microbiota-gut-brain axis in dementia including the role of gut microbiota in pathogenesis, underlying mechanisms and biological factors influencing the microbiome-gut-brain axis. The review includes potential therapeutic approaches to recondition gut microbiota to alleviate disease progression.

Alzheimer's disease (AD) is a fatal progressive neurodegenerative disease. Despite tremendous research efforts to understand this complex disease, the exact pathophysiology of the disease is not completely clear. Recently, anti-A $\beta$  antibodies have been shown to remove amyloid from the brain and slow the clinical progression of mild dementia by ~30%. However, exploring alternative strategies is crucial to understanding and developing more effective therapeutic interventions. In recent years, the microbiota-gut-brain axis has received significant attention in the AD field. Numerous studies have suggested that alterations in the gut microbiota composition are associated with the progression of AD, and several underlying mechanisms have been proposed. However, studies in this area are still in their infancy, and many aspects of this field are just beginning to be explored and understood. Gaining a deeper understanding of the intricate interactions and signaling pathways involved in the microbiota-AD interaction is crucial for optimizing therapeutic strategies targeting gut microbiota to positively impact AD. In this review, we aim to summarize the current understanding of the microbiota-gut-brain axis in AD. We will discuss the existing evidence regarding the role of gut microbiota in AD pathogenesis, suggested underlying mechanisms, biological factors influencing the microbiome-gut-brain axis in AD, and remaining questions in the field. Last, we will discuss potential therapeutic approaches to recondition the community of gut microbiota to alleviate disease progression. An ongoing exploration of the gut-brain axis and the development of microbiota-based therapies hold the potential for advancing AD management in the future.

### Dairy Intake and Risk of Cognitive Decline and Dementia: A Systematic Review and Dose-Response Meta-Analysis of Prospective Studies

Fanny Viloz, Tommaso Filippini, Natalia Ortega, Doris Kopp-Heim, Trudy Voortman, Manuel R Blum, Cinzia Del Giovane, et. al. *Adv Nutr*. 2024 Jan;15(1):100160. doi: 10.1016/j.advnut.2023.100160. [Article link](#)

**Significance:** This study reports a nonlinear inverse association between dairy intake and cognitive decline or dementia, dependent on dairy types and population characteristics. Further studies are needed that include a wider range of intake and types of dairy products to confirm the role of dairy intake in preventing cognitive decline.

Dairy intake may influence cognition through several molecular pathways. However, epidemiologic studies yield inconsistent results, and no dose-response meta-analysis has been conducted yet. Therefore, we performed a systematic review with a dose-response meta-analysis about the association between

dairy intake and cognitive decline or incidence of dementia. We investigated prospective studies with a follow-up  $\geq 6$  mo on cognitive decline or dementia incidence in adults without known chronic conditions through a systematic search of Embase, Medline, Cochrane Library, Web of Science, and Google Scholar from inception to 11 July 2023. We evaluated the dose-response association using a random-effects model. We identified 15 eligible cohort studies with  $>300,000$  participants and a median follow-up of 11.4 y. We observed a negative nonlinear association between cognitive decline/dementia incidence and dairy intake as assessed through the quantity of consumption, with the nadir at  $\sim 150$  g/d (risk ratio: 0.88; 95% confidence interval: 0.78, 0.99). Conversely, we found an almost linear negative association when we considered the frequency of consumption (risk ratio for linear trend: 0.84; 95% confidence interval: 0.77, 0.92 for 1 time/d increase of dairy products). Stratified analysis by dairy products showed different shapes of the association with linear inverse relationship for milk intake, whereas possibly nonlinear for cheese. The inverse association was limited to Asian populations characterized by generally lower intake of dairy products, compared with the null association reported by European studies. In conclusion, our study suggests a nonlinear inverse association between dairy intake and cognitive decline or dementia, also depending on dairy types and population characteristics, although the heterogeneity was still high in overall and several subgroup analyses. Additional studies should be performed on this topic, including a wider range of intake and types of dairy products, to confirm a potential preventing role of dairy intake on cognitive decline and identify ideal intake doses.

## Lipids

### High-Fat Diets in Animal Models of Alzheimer's Disease: How Can Eating Too Much Fat Increase Alzheimer's Disease Risk?

Josue Valentin-Escalera, Manon Leclerc, Frédéric Calon. *J Alzheimers Dis.* 2024;97(3):977-1005. doi: 10.3233/JAD-230118. [Article link](#)

**Significance:** This narrative review of animal studies found that in spite of broad methodological variations, diets highly enriched in saturated fat induced metabolic defects, cognitive impairment and burdens. Together they suggest that reducing excessive intake of saturated fat would help to lower the incidence of dementia.

High dietary intake of saturated fatty acids is a suspected risk factor for neurodegenerative diseases, including Alzheimer's disease (AD). To decipher the causal link behind these associations, high-fat diets (HFD) have been repeatedly investigated in animal models. Preclinical studies allow full control over dietary composition, avoiding ethical concerns in clinical trials. The goal of the present article is to provide a narrative review of reports on HFD in animal models of AD. Eligibility criteria included mouse models of AD fed a HFD defined as  $> 35\%$  of fat/weight and western diets containing  $> 1\%$  cholesterol or  $> 15\%$  sugar. MEDLINE and Embase databases were searched from 1946 to August 2022, and 32 preclinical studies were included in the review. HFD-induced obesity and metabolic disturbances such as insulin resistance and glucose intolerance have been replicated in most studies, but with methodological variability. Most studies have found an aggravating effect of HFD on brain A $\beta$  pathology, whereas tau pathology has been much less studied, and results are more equivocal. While most reports show HFD-induced impairment on cognitive behavior, confounding factors may blur their interpretation. In summary, despite conflicting results, exposing rodents to diets highly enriched in saturated fat induces not only metabolic defects, but also cognitive impairment often accompanied by aggravated neuropathological markers, most notably A $\beta$  burden. Although there are important variations between methods, particularly the lack of diet characterization, these studies collectively suggest that excessive intake of saturated fat should be avoided in order to lower the incidence of AD.

## Sodium

### Salty Subjects: Unpacking Racial Differences in Salt-Sensitive Hypertension

Soolim Jeong, Stacy D Hunter, Marc D Cook, Gregory J Grosicki, Austin T Robinson. *Curr Hypertens Rep.* 2024 Jan;26(1):43-58. doi: 10.1007/s11906-023-01275-z. [Article link](#)

**Significance:** This review provides current perspectives on racial disparities and salt sensitivity, including potential underlying mechanisms, and social and health behavioral determinants that impact salt sensitivity and blood pressure.

**Purpose of Review:** To review underlying mechanisms and environmental factors that may influence racial disparities in the development of salt-sensitive blood pressure. **Recent Findings:** Our group and others have observed racial differences in diet and hydration, which may influence salt sensitivity. Dietary salt elicits negative alterations to the gut microbiota and immune system, which may increase hypertension risk, but little is known regarding potential racial differences in these physiological responses. Antioxidant supplementation and exercise offset vascular dysfunction following dietary salt, including in Black adults. Furthermore, recent work proposes the role of racial differences in exposure to social determinants of health, and differences in health behaviors that may influence risk of salt sensitivity. Physiological and environmental factors contribute to the mechanisms that manifest in racial differences in salt-sensitive blood pressure. Using this information, additional work is needed to develop strategies that can attenuate racial disparities in salt-sensitive blood pressure.

## Gut Health

### Nutrition and Disorders of Gut-Brain Interaction

Emidio Scarpellini, Lukasz Michaja Balsiger, Bert Broeders, Karen Van Den Houte, Karen Routhiaux, Karlien Raymenants, Florencia Carbone, et. al. *Nutrients.* 2024 Jan 4;16(1):176. doi: 10.3390/nu16010176. [Article link](#)

**Significance:** Food volume, nutritive and chemical composition, and malabsorption are associated with symptom generation in disorders of gut-brain interaction.

**Background:** Disorders of gut-brain interaction (DGBIs) have a complex pathophysiology that is often characterized by a relationship between food ingestion and triggering of symptoms. Understanding of the underlying mechanisms and the role of nutrients as a therapeutic target are rapidly evolving.

**Aims and Methods:** We performed a narrative review of the literature using the following keywords, their acronyms, and their associations: nutrients, disorders of gut-brain interaction; functional dyspepsia; malabsorption; irritable bowel syndrome; diarrhea; constipation. **Results:** Functional dyspepsia displayed a significant correlation between volume, fat and/or wheat abundance, chemical composition of ingested food and symptoms of early satiety, fullness, and weight loss. Carbohydrate malabsorption is related to enzyme deficiency throughout the GI tract. Food composition and richness in soluble vs. non-soluble fibers is related to constipation and diarrhea. The elimination of fermentable oligo-, di-, monosaccharides and polyols (FODMAPs) has a significant and non-unidirectional impact on irritable bowel syndrome (IBS) symptoms. **Conclusions:** Food volume, nutritive and chemical composition, and its malabsorption are associated with symptom generation in DGBIs. Further multicenter, randomized-controlled clinical trials are needed to clarify the underlying pathophysiology.

### The Impact of Live Dietary Microbes on Health: A Scoping Review

Ajay Iyer, Arghya Mukherjee, Beatriz Gómez-Sala, Eibhlís M. O'Connor, John G. Kenny, Paul D. Cotter. 04 January 2024. doi.org/10.1111/1750-3841.16893. [Article link](#)

**Significance:** Eliciting the benefits of dietary microbes on human health remains challenging due to methodological and analytical limitations. More high-quality research, including validated fecal measurements, is needed to better define the importance of dietary microbes in maintaining and promoting general health and wellbeing.



This paper was supported by IAFNS' [Nutrition for Gut Health Committee](#)

A systematic approach to collect, peruse, and summarize the available information relating to the potential benefits of consuming dietary microbes was pursued in this scoping review. This review focused on the research endpoints, experimental designs, and microbial exposure in experimental as well as observational research work. Using a structured- set of keywords, scientific databases were systematically searched to retrieve publications reporting outcomes pertaining to the use of dietary microbes in healthy, nonpatient populations. Searches were further tailored to focus on eight different health categories, namely, "antibiotic associated diarrhea" (AAD), "gastrointestinal health" (GIH), "immunological health" (ImH), "cardiovascular health and metabolic syndrome" (CvHMS), "cancer prevention" (CanPr), "respiratory health" (ReH), "weight management" (WtMgt), and "urogenital health" (UrGH). Quality of evidence available in each publication was assessed using the Jadad scoring system. The search yielded 228 relevant publications describing 282 experimental cases comprising 62 research endpoints overall. Older population groups with a median age of 39 years were associated with positive outcomes. More high-quality research is required investigating the role of dietary microbes in maintaining general health, particularly in the health categories of UrGH, WtMgt, and CanPr.

## Emerging Science Areas

Emerging Area: Nanotechnology and Supplements

### *In vitro* and *in vivo* Genotoxicity Evaluation of ALP1018, A Nanomineral Food Supplement

Patience Mahoro, Euna Kwon, Yun-Soon Kim, Jung-Min Bae, Soon-Ae Kim, Junlae Cho, Youn-Soo Cha, et. al. Food Chem Toxicol. 2024 Epub Jan 6:184:114437. doi: 10.1016/j.fct.2024.114437. [Article link](#)

**Significance:** The use of nano-based supplements is receiving increased interest. A study using a nanomineral supplement was found not to interfere with DNA metabolism and has no mutagenic or genotoxic potential in safety tests.

The use of nano-based dietary supplements is increasing around the world, as nanotechnology can help enhance nutrient bioavailability. ALP1018 is a newly developed iron-zinc complex supplement designed as a nanoformulation to improve the efficacy of iron and zinc supplementation. However, safety concerns have been raised, as there is no clear evaluation of ALP1018 toxicity. The goal of this study was to determine the potential mutagenicity and genotoxicity of ALP1018 through three standard screenings: the Ames test, which evaluates bacterial reverse mutations; the *in vitro* test of chromosomal aberration in Chinese hamster lung cells; and the *in vivo* micronucleus assay using ICR mice. ALP1018 showed no mutagenic effect, as no increase was observed in the presence or absence of metabolic activation (S9 mix) in revertant colonies on all the bacterial strains used in the Ames test. No structural chromosomal abnormalities were observed in the presence or absence of the S9 mix in mammalian cells used in the chromosomal aberration assay. In the micronucleus test, the frequency of micronucleated polychromatic erythrocytes was not significantly increased in mouse bone marrow cells. Based on these findings, we can conclude that ALP1018 is safe to use and has no mutagenic or genotoxic potential.

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February 15, 2024.

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