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# Nutrition Briefs

## Dietary Patterns

### Perspective: Plant-Based Eating Pattern for Type 2 Diabetes Prevention and Treatment: Efficacy, Mechanisms, and Practical Considerations

Jardine MA, Kahleova H, Levin SM, Ali Z, Trapp CB, Barnard ND. *Advances in Nutrition*, 10 June 2021, nmab063 https://doi.org/10.1093/advances/nmab063. **Article link**

**Significance:** A plant-based eating pattern is beneficial for T2D prevention and treatment, as a result of improvement in insulin sensitivity and B-cells functions and weight reduction. Success can be further enhanced by nutritional education and medication adjustments.

A plant-based eating pattern is associated with a reduced risk of developing type 2 diabetes and is highly effective in its treatment. Diets that emphasize whole grains, vegetables, fruits, and legumes and exclude animal products improve blood glucose concentrations, body weight, plasma lipid concentrations, and blood pressure and play an important role in reducing the risk of cardiovascular and microvascular complications. This article reviews scientific evidence on the effects of plant-based diets for the prevention and treatment of type 2 diabetes. The mechanisms by which plant-based diets improve body weight, insulin sensitivity, and β-cell function are described. Practical considerations including education, nutrition adequacy, and adjusting medications will enhance the success of patients who have diabetes.

## Proteins

### The Impact of Protein Type on Phosphorus Intake, Serum Phosphate Concentrations, and Nutrition Status in Adults with Chronic Kidney Disease: A Critical Review

Picard K, Mager DR, Richard C. *Advances in Nutrition*, 10 June 2021 nmab062, https://doi.org/10.1093/advances/nmab062. **Article link**

**Significance:** A critical review found inconclusive evidence supporting plant-protein food restrictions for individuals at risk of chronic kidney diseases. A reevaluation of this guidance is suggested, to be supported by longer-term intervention trials with larger sample sizes.

Lower phosphorus intake to prevent hyperphosphatemia for those with chronic kidney disease (CKD) is often recommended. Plant proteins are frequently restricted for their high phosphorus content despite having lower bioavailability. To summarize the evidence on protein type and dietary phosphorus intake, serum phosphate concentrations, and nutritional adequacy in adults with CKD, a search in MEDLINE via Ovid was conducted. Citation lists were reviewed to identify any additional articles. Sixteen articles were included—7 intervention (n = 290) and 9 observational (n = 4933). All intervention trials reported high-plant-protein diets provided adequate protein and adhered to low phosphorus diet guidelines. All intervention trials reported higher plant-protein intake was associated with lower serum phosphate; however, only 2 achieved statistical significance. For observational studies, 2 reported that higher proportions of plant to animal protein resulted in lower phosphorus intake but equivalent serum phosphate concentrations. Two reported that plant protein and animal protein had equivalent correlation values to phosphorus intake and no correlation to serum phosphate concentrations. One trial reported lower total phosphorus and protein intake among those who consumed more plant proteins but did not examine serum concentrations. Four reported lower serum phosphate concentrations among those who consumed more plant proteins but did not report dietary phosphorus intake. Of the observational studies that reported on protein intake, all reported lower protein intake among those with higher versus lower plant-protein intake. BMI tended to be lower among those consuming more plant protein. There was not a consistent relation between protein type and albumin

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concentrations. Routine restriction of plant-protein foods to prevent hyperphosphatemia in CKD would likely benefit from re-evaluation, as evidence does not suggest that higher plant-protein intake leads to higher serum phosphate concentrations or worse nutritional status, although longer-duration intervention trials with larger sample sizes appear to be warranted.

## Lipids

### Using an Erythrocyte Fatty Acid Fingerprint to Predict Risk of All-Cause Mortality: the Framingham Offspring Cohort

McBurney MI, Tintle NL, Vasan RS, Sala-Vila A, Harris WS. *The American Journal of Clinical Nutrition*, 16 June 2021 nqab195, https://doi.org/10.1093/ajcn/nqab195. **Article link**

**Significance:** In this community-based population of 2,240 subjects in their mid-60s, RBC Fatty Acid patterns were as predictive of risk for death during the next 11 years as standard risk factors (age, sex, total cholesterol, HDL cholesterol, hypertension treatment, systolic blood pressure, smoking status, and prevalent diabetes). This paper was supported by IAFNS Dietary Lipids Committee.

This work was supported by the IAFNS **Dietary Lipids Committee.**

**Background**: RBC long-chain omega-3 (n–3) fatty acid (FA) percentages (of total fatty acids) are associated with lower risk for total mortality, but it is unknown if a suite of FAs could improve risk prediction. **Objectives**: The objective of this study was to compare a combination of RBC FA levels with standard risk factors for cardiovascular disease (CVD) in predicting risk of all-cause mortality. **Methods**: Framingham Offspring Cohort participants without prevalent CVD having RBC FA measurements and relevant baseline clinical covariates (n = 2240) were evaluated during 11 y of follow-up. A forward, stepwise approach was used to systematically evaluate the association of 8 standard risk factors (age, sex, total cholesterol, HDL cholesterol, hypertension treatment, systolic blood pressure, smoking status, and prevalent diabetes) and 28 FA metrics with all-cause mortality. A 10-fold cross-validation process was used to build and validate models adjusted for age and sex. **Results**: Four of 28 FA metrics [14:0, 16:1n–7, 22:0, and omega-3 index (O3I; 20:5n–3 + 22:6n–3)] appeared in ≥5 of the discovery models as significant predictors of all-cause mortality. In age- and sex-adjusted models, a model with 4 FA metrics was at least as good at predicting all-cause mortality as a model including the remaining 6 standard risk factors (C-statistic: 0.778; 95% CI: 0.759, 0.797; compared with C-statistic: 0.777; 95% CI: 0.753, 0.802). A model with 4 FA metrics plus smoking and diabetes (FA + Sm + D) had a higher C-statistic (0.790; 95% CI: 0.770, 0.811) compared with the FA ($P < 0.01$) or Sm + D models alone (C-statistic: 0.766; 95% CI: 0.739, 0.794; $P < 0.001$). A variety of other highly correlated FAs could be substituted for 14:0, 16:1n–7, 22:0, or O3I with similar predicted outcomes. **Conclusions:** In this community-based population in their mid-60s, RBC FA patterns were as predictive of risk for death during the next 11 y as standard risk factors. Replication is needed in other cohorts to validate this FA fingerprint as a predictor of all-cause mortality.

## Carbohydrates

### Effect of Carbohydrate-Restricted Dietary Interventions on LDL Particle Size and Number in Adults in the Context of Weight Loss or Weight Maintenance: a Systematic Review and Meta-Analysis

Falkenhain K, Roach LA, McCreary S, McArthur E, Weiss EJ, Francois ME, Little JP. *The American Journal of Clinical Nutrition*, 22 June 2021 nqab212, https://doi.org/10.1093/ajcn/nqab212. **Article link**

**Significance:** A review of 38 RCT showed an association between dietary carbohydrate restriction and increase in LDL peak particle size and decline in LDL-P, an effect partly due to differences in weight loss between intervention groups and a shift from small dense to larger LDL subclasses.

**Background**: LDL particle size and number (LDL-P) are emerging lipid risk factors. Nonsystematic reviews have suggested that diets lower in carbohydrates and higher in fats may result in increased LDL particle size when compared with higher-carbohydrate diets. **Objectives:** This study aimed to systematically review available evidence and conduct meta-analyses of studies addressing the association of carbohydrate restriction with LDL particle size and LDL-P. **Methods**: We searched 6 electronic databases on 4 January, 2021 for randomized trials of any length that reported on dietary carbohydrate restriction (intervention) compared with higher carbohydrate intake (control). We calculated standardized mean differences (SMDs) in LDL particle size and LDL-P between the intervention and control groups of eligible studies, and pooled effect sizes using random-effects models. We performed prespecified subgroup analyses and examined the effect of potential explanatory factors. Internal validity and publication bias were assessed using Cochrane's risk-of-bias tool and funnel plots, respectively.

Studies that could not be meta-analyzed were summarized qualitatively. **Results:** This review summarizes findings from 38 randomized trials including a total of 1785 participants. Carbohydrate-restricted dietary interventions were associated with an increase in LDL peak particle size (SMD = 0.50; 95% CI: 0.15, 0.86; P < 0.01) and a reduction in LDL-P (SMD = −0.24; 95% CI: −0.43, −0.06; P = 0.02). The effect of carbohydrate-restricted dietary interventions on LDL peak particle size appeared to be partially explained by differences in weight loss between intervention groups and exploratory analysis revealed a shift from small dense to larger LDL subclasses. No statistically significant association was found between carbohydrate-restricted dietary interventions and mean LDL particle size (SMD = 0.20; 95% CI: −0.29, 0.69; P = 0.37). **Conclusions**: The available evidence indicates that dietary interventions restricted in carbohydrates increase LDL peak particle size and decrease the numbers of total and small LDL particles.

### Hepatic Energy Metabolism Underlying Differential Lipidomic Responses to High-Carbohydrate and High-Fat Diets in Male Wistar Rats

Dankel SN, Bjørndal B, Lindquist C, Grinna ML, Rossmann CR, Bohov P, et. al. *The Journal of Nutrition*, nxab178, https://doi.org/10.1093/jn/nxab178 Published: 16 June 2021. **Article link**

**Significance:** Differential hepatic lipidomic responses to high fat, low carbohydrate (HF) or high carbohydrate, low fat (HC) diet was reported in a male rat study. HF increased hepatic fatty acid content, independent of hepatic mitochondrial fatty acid oxidation, while HC increased specific fatty acids production via hepatic lipogenesis, resulting in higher plasma TG and total fatty acids compared with high-fat feeding.

**Background:** Low-carbohydrate diets are suggested to exert metabolic benefits by reducing circulating triacylglycerol (TG) concentrations, possibly by enhancing mitochondrial activity. **Objective**: We aimed to elucidate mechanisms by which dietary carbohydrate and fat differentially affect hepatic and circulating TG, and how these mechanisms relate to fatty acid composition. **Methods:** Six-week-old, ~300 g male Wistar rats were fed a high-carbohydrate, low-fat [HC; 61.3% of energy (E%) carbohydrate] or a low-carbohydrate, high-fat (HF; 63.5 E% fat) diet for 4 wk. Parameters of lipid metabolism and mitochondrial function were measured in plasma and liver, with fatty acid composition (GC), high-energy phosphates (HPLC), carnitine metabolites (HPLC-MS/MS), and hepatic gene expression (qPCR) as main outcomes. **Results**: In HC-fed rats, plasma TG was double and hepatic TG 27% of that in HF-fed rats. The proportion of oleic acid (18:1n−9) was 60% higher after HF vs. HC feeding while the proportion of palmitoleic acid (16:1n−7) and vaccenic acid (18:1n−7), and estimated activities of stearoyl-CoA desaturase, SCD-16 (16:1n−7/16:0), and de novo lipogenesis (16:0/18:2n−6) were 1.5–7.5-fold in HC vs. HF-fed rats. Accordingly, hepatic expression of fatty acid synthase (Fasn) and acetyl-CoA carboxylase (Acaca/Acc) was strongly upregulated after HC feeding, accompanied with 8-fold higher FAS activity and doubled ACC activity. There were no differences in expression of liver-specific biomarkers of mitochondrial biogenesis and activity (Cytc, Tfam, Cpt1, Cpt2, Ucp2, Hmgcs2); concentrations of ATP, AMP, and energy charge; plasma carnitine/acylcarnitine metabolites; or peroxisomal fatty acid oxidation. **Conclusions**: In male Wistar rats, dietary carbohydrate was converted into specific fatty acids via hepatic lipogenesis, contributing to higher plasma TG and total fatty acids compared with high-fat feeding. In contrast, the high-fat, low-carbohydrate feeding increased hepatic fatty acid content, without affecting hepatic mitochondrial fatty acid oxidation**.**

## Low- and No-Calorie Sweeteners

### Sugar-Sweetened Beverages, Artificially Sweetened Beverages, and Breast Cancer Risk: Results From 2 Prospective US Cohorts

Romanos-Nanclares A, Collins LC, Hu FB, Willett WC, Rosner BA, Toledo E, Eliassen AH. *The Journal of Nutrition*, 10 June 2021 nxab172, https://doi.org/10.1093/jn/nxab172. **Article link**

**Significance:** A study examining 11,379 breast cancer cases during 4,655,153 person-years of follow-up reported that intake of SSBs or ASBs was not significantly associated with total breast cancer risk. However, the study found a suggestive interaction by BMI between intake of SSBs and overall cancers, implying a slightly higher risk of breast cancer among lean women.

**Background:** Whether consumption of sugar-sweetened beverages (SSBs) or artificially sweetened beverages (ASBs) is associated with the risk of breast cancer is of public health interest. Objectives: We sought to evaluate associations between consumption of SSBs and ASBs and risks of total and subtype-specific breast cancer. **Methods:** We followed 82,713 women from the Nurses' Health Study (1980 to 2016) and 93,085 women from the Nurses' Health Study II (1991 to 2017). Cumulatively averaged intakes of SSBs and ASBs from FFQs were tested for associations with incident breast cancer cases and subtypes using Cox regression models. We also evaluated the associations stratified by menopausal status, physical

activity, BMI, and alcohol intake. **Results**: We documented 11,379 breast cancer cases during 4,655,153 person-years of follow-up. Consumption of SSBs or ASBs was not associated with total breast cancer risk: pooled HRs comparing extreme categories (≥1/day compared with <1/month) were 1.03 (95% CI, 0.95–1.12) and 0.96 (95% CI, 0.91–1.02), respectively. We observed a suggestive interaction by BMI using pooled data (P-interaction = 0.08), where a modestly higher risk of breast cancer with each serving per day increment of SSBs was found in lean women (HR, 1.06; 95% CI, 1.01–1.11) but not among overweight or obese women (HR, 1.00; 95% CI, 0.95–1.06). Moreover, in the pooled, fully adjusted analysis, compared to infrequent consumers (<1/month), those who consumed ≥1 serving of ASBs per day had a lower risk of luminal A breast tumors (HR, 0.90; 95% CI, 0.80–1.01; P-trend = 0.02). **Conclusions**: Although no significant associations were observed overall, consumption of SSBs was associated with a slightly higher risk of breast cancer among lean women. This finding could have occurred by chance and needs confirmation. Our findings also suggest no substantial increase in the risk of breast cancer with consumption of ASBs.

## Bioactives

### (–)-Epicatechin and Anthocyanins Modulate GLP-1 Metabolism: Evidence from C57BL/6J Mice and GLUTag Cells

Cremonini E, Daveri E, Mastaloudis A, Oteiza PI. *The Journal of Nutrition*, Volume 151, Issue 6, June 2021, Pages 1497–1506, https://doi.org/10.1093/jn/nxab029. **Article link**

**Significance:** EC and ACs regulate different steps in GLP-1 metabolic pathway. These findings in mice and cell studies demonstrate the beneficial actions of these flavonoids in maintaining intestinal and glucose homeostasis through modulation of GLP-1 metabolism.

**Background**: Generated in intestinal L cells through cleavage of proglucagon (Gcg), glucagon-like peptide 1 (GLP-1) is secreted and rapidly inactivated by dipeptidyl peptidase IV (DPP-IV). GLP-1 regulates insulin secretion and overall glucose homeostasis. The capacity of dietary bioactives to increase GLP-1 circulating levels, and therefore increase insulin secretion and glucose metabolism, has gained significant interest of late. **Objectives:** We evaluated the effects of (–)-epicatechin (EC) and different anthocyanins (ACs) and AC metabolites on GLP-1 metabolism in mice and on GLUTag cells. **Methods**: We fed 6-week-old C57BL/6J male mice a control diet or a control diet supplemented with either 40 mg AC or 20 mg EC/kg body weight for 14 weeks (AC) or 15 weeks (EC). Intestinal mRNA levels of Gcg and Dpp-iv were measured. In vitro, GLUTag cells were incubated in the presence or absence of different ACs, the AC metabolite protocatechuic acid (PCA), and EC. GLP-1 secretion and the main pathways involved in its release were assessed. **Results**: Long-term supplementation with EC or AC increased mouse GLP-1 plasma concentrations (55% and 98%, respectively; $P < 0.05$). In mice, 1) EC and AC increased Gcg mRNA levels in the ileum (91%) and colon (41%), respectively ($P < 0.05$); and 2) AC lowered ileum Dpp-iv mRNA levels (35%), while EC decreased plasma DPP-IV activity (15%; $P < 0.05$). In GLUTag cells, 1) cyanidin, delphinidin, PCA, and EC increased GLP-1 secretion (53%, 33%, 53%, and 68%, respectively; $P < 0.05$); and 2) cyanidin, delphinidin, EC, and PCA increased cyclin adenosine monophosphate levels (25–50%; $P < 0.05$) and activated protein kinase A (PKA; 100%, 50%, 80%, and 86%, respectively; $P < 0.05$). **Conclusions:** In mice, EC and ACs regulated different steps in GLP-1 regulation, leading to increased plasma GLP-1. Cyanidin, delphinidin, PCA, and EC promoted GLP-1 secretion from GLUTag cells by activating the PKA-dependent pathway. These findings support the beneficial actions of these flavonoids in sustaining intestinal and glucose homeostasis through the modulation of the GLP-1 metabolism.

## Sodium

### Association Between the Urinary Sodium to Potassium Ratio and Blood Pressure in Adults: A Systematic Review and Meta-Analysis

Ndanuko RN, Ibrahim R, Hapsari RA, Neale EP, Raubenheimer D, Charlton KE. *Advances in Nutrition*, 10 June 2021, nmab036, https://doi.org/10.1093/advances/nmab036. **Article link**

**Significance:** A systematic review of current body of evidence correlates lower 24-h UNa: K ratio with lower BP in adults, supporting current dietary strategy to increase potassium and reduce sodium intakes that would benefit blood pressure control.

While sodium and potassium are individually important for blood pressure (BP) regulation, the relative contribution of sodium to potassium intake has not been sufficiently investigated. This study aimed to evaluate the association between urinary sodium to potassium ratio (UNa: K) and systolic and diastolic BP in adults. A systematic review (PROSPERO;

CRD42016035296) was conducted and was reported according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Three scientific databases (MEDLINE, Scopus, Web of Science) were searched to March 2020 while reference lists of included articles were further hand-searched. Randomized controlled trials (RCT), cohort and cross-sectional studies that assessed 24-h urinary excretion in adults were included. Data from eligible studies were extracted and summarized. Random effects meta-analysis was conducted on RCT data to assess standardized mean differences (SMD) in systolic and diastolic BP according to 24-h UNa: K. Thirty-nine studies were included. Meta-analysis of 5 RCTs found a lower UNa: K ratio to be associated with a significantly greater reduction in systolic and diastolic BP compared with a higher UNa: K ratio [SMD: −1.09 (95% CI: −1.91, −0.28) mmHg and −1.42 (95% CI: −2.24, −0.59) mmHg, respectively]. Heterogeneity between RCTs was observed in systolic and diastolic BP ($I2 = 97\%$, $P < 0.0001$ and $I2 = 98\%$, $P < 0.0001$, respectively). The current body of evidence demonstrates that a lower 24-h UNa: K ratio is associated with lower BP in adults. Dietary strategies to achieve an increase in potassium while at the same time lowering sodium would be beneficial in lowering BP.

## Gut Microbiome

### Plant-Based Diet Index and Metabolic Risk in Men: Exploring the Role of the Gut Microbiome

Li Y, Wang DD, Satija A, Ivey KL, Li J, Wilkinson JE, et. al. *The Journal of Nutrition*, 10 June 2021 nxab173, https://doi.org/10.1093/jn/nxab175. **Article link**

**Significance:** Older men may benefit from adhering to a healthy plant-based diet to reduce CVD risks, mediated through a higher abundance of multiple gut microbial species, including *B. cellulosilyticus, E. eligens*, and changes in amino acid metabolism and pyruvate fermentation.

**Objectives**: We aimed to investigate the interrelations between hPDI, gut microbiome, and cardiometabolic risk markers. **Methods**: hPDI was derived from dietary assessments by a validated FFQ and was examined in relation to metagenomic profiles of 911 fecal samples collected from 303 men aged 71 ± 4 y with an average BMI (in kg/m2) of 25.2 ± 3.6 in the Men's Lifestyle Validation Study. Principal coordinate (PCo) analysis based on Bray–Curtis dissimilarity was conducted, and interactions between hPDI and PCo were examined by using a metabolic risk score composed of blood lipids, BMI, and glycated hemoglobin. **Results**: After multivariable adjustment, hPDI was significantly associated with the relative abundance of 7 species and 9 pathways. In particular, higher hPDI was significantly associated with a higher relative abundance of *Bacteroides cellulosilyticus* and *Eubacterium eligens*, amino acid biosynthesis pathways (L-isoleucine biosynthesis I and III and L-valine biosynthesis), and the pathway of pyruvate fermentation to isobutanol. A favorable association between hPDI and the metabolic risk score was more pronounced among men with a higher PCo characterized by higher abundance of *Bacteroides uniformis* and lower abundance of *Prevotella copri*. At the individual species level, a similar interaction was also observed between hPDI and *P. copri*, as well as with *Clostridium clostridioforme* or *Blautia hydrogenotrophica* (all P-interaction < 0.01). **Conclusion**: A greater adherence to a healthy plant-based diet by older men was associated with a microbial profile characterized by a higher abundance of multiple species, including *B. cellulosilyticus* and *E. eligens,* as well as pathways in amino acid metabolism and pyruvate fermentation. In addition, inverse associations between healthy plant-based diet and human metabolic risk may partially depend on microbial compositions.