Dietary Patterns

Vegetarian-Based Dietary Patterns and Their Relation With Inflammatory and Immune Biomarkers: A Systematic Review and Meta-Analysis


Significance: This systematic review and meta-analysis found an inverse association between vegetarian-based diet patterns and inflammatory markers.

Dietary patterns with substantial proportions of energy from plant sources have been associated with favorable biomarkers of low-grade inflammation. Less is known of the relation between vegetarian-based dietary patterns and inflammatory and immune markers (C-reactive protein, tumour necrosis factor α, fibrinogen, natural killer cells, leukocytes, lymphocytes, thrombocytes, interleukins, and immunoglobulins). PubMed, Medline, and Cochrane scientific databases were searched to identify relevant studies. Random effects meta-analyses were conducted to assess the weighted mean differences (WMDs) for each outcome variable between vegetarian and non-vegetarian groups. Thirty observational and 10 intervention studies were included in the review. Pooled effects of vegetarian-based dietary patterns were associated with significantly lower concentrations of CRP (WMD: -0.61 mg/L; 95% CI: -0.91, -0.32 mg/L; P = 0.0001), fibrinogen (WMD: -0.22 g/L; 95% CI: -0.41, -0.04 mg/L; P = 0.02), and total leukocyte (WMD: -0.62 × 10³/μL; 95% CI -1.13 × 10³, -0.10 × 10³/μL; P = 0.02) compared with those following non-vegetarian dietary patterns in observational studies. Insufficient data were identified for a meta-analysis of intervention studies. This study provides evidence that vegetarian-based dietary patterns are associated with lowered serum C-reactive protein, fibrinogen, and total leukocyte concentrations. Future research should focus on large-scale intervention trials, contrasting differences in inflammation and immune status and function between vegetarian and non-vegetarian-based populations.

Energy Expenditure Methodology

Methodologic Considerations for Measuring Energy Expenditure Differences Between Diets Varying in Carbohydrate Using the Doubly Labeled Water Method


Significance: This study highlights important methodological considerations for estimating energy expenditure using doubly labeled water.

Background: Low-carbohydrate diets have been reported to significantly increase human energy expenditure when measured using doubly labeled water (DLW) but not by respiratory chambers. Although DLW may reveal true physiological differences undetected by respiratory chambers, an alternative possibility is that the expenditure differences resulted from failure to correctly estimate the respiratory quotient (RQ) used in the DLW calculations. Objective: To examine energy expenditure differences between isocaloric diets varying widely in carbohydrate and to quantitatively compare DLW data with respiratory chamber and body composition measurements within an energy balance framework. Design: DLW measurements were obtained during
the final 2 wk of month-long baseline (BD; 50% carbohydrate, 35% fat, 15% protein) and isocaloric ketogenic diets (KD; 5% carbohydrate, 80% fat, 15% protein) in 17 men with a BMI of 25–35 kg/m². Subjects resided 2 d/wk in respiratory chambers to measure energy expenditure (EEchamber). DLW expenditure was calculated using chamber-determined RQ either unadjusted (EEDLW) or adjusted (EEDLWΔRQ) for net energy balance using diet-specific coefficients. Accelerometers measured physical activity. Body composition changes were measured by dual-energy X-ray absorptiometry (DXA) which were combined with energy intake measurements to calculate energy expenditure by balance (EEbal). Results: After transitioning from BD to KD, neither EEchamber nor EEbal were significantly changed (ΔEEdLWchamber = 24 ± 30 kcal/d; P = 0.43 and ΔEEEdLWbal = −141 ± 118 kcal/d; P = 0.25). Similarly, physical activity (−5.1 ± 4.8%; P = 0.3) and exercise efficiency (−1.6 ± 2.4%; P = 0.52) were not significantly changed. However, EEDLW was 209 ± 83 kcal/d higher during the KD (P = 0.023) but was not significantly increased when adjusted for energy balance (EEDLWΔRQ = 139 ± 89 kcal/d; P = 0.14). After removing 2 outliers whose EEDLW were incompatible with other data, EEDLW was marginally increased during the KD by 126 ± 62 kcal/d (P = 0.063) and EEDLWΔRQ was only 46 ± 65 kcal/d higher (P = 0.49). Conclusions: DLW calculations failing to account for diet-specific energy imbalance effects on RQ erroneously suggest that low-carbohydrate diets substantially increase energy expenditure. This trial was registered at clinicaltrials.gov as NCT01967563.

Protein

A Meta-Analysis of 46 Studies Identified by the FDA Demonstrates That Soy Protein Decreases Circulating LDL and Total Cholesterol Concentrations in Adults


Significance: The results from this meta-analysis support the use of the FDA heart health claim for soy protein.

Background: Certain plant foods (nuts and soy protein) and food components (viscous fibers and plant sterols) have been permitted by the FDA to carry a heart health claim based on their cholesterol-lowering ability. The FDA is currently considering revoking the heart health claim for soy protein due to a perceived lack of consistent LDL cholesterol reduction in randomized controlled trials. Objective: We performed a meta-analysis of the 46 controlled trials on which the FDA will base its decision to revoke the heart health claim for soy protein. Methods: We included the 46 trials on adult men and women, with baseline circulating LDL cholesterol concentrations ranging from 110 to 201 mg/dL, as identified by the FDA, that studied the effects of soy protein on LDL cholesterol and total cholesterol (TC) compared with non-soy protein. Two independent reviewers extracted relevant data. Data were pooled by the generic inverse variance method with a random effects model and expressed as mean differences with 95% CI. Heterogeneity was assessed and quantified. Results: Of the 46 trials identified by the FDA, 43 provided data for meta-analyses. Of these, 41 provided data for LDL cholesterol, and all 43 provided data for TC. Soy protein at a median dose of 25 g/d during a median follow-up of 6 wk decreased LDL cholesterol by 4.76 mg/dL (95% CI: −6.71, −2.80 mg/dL, P < 0.0001; I² = 55%, P < 0.0001) and decreased TC by 6.41 mg/dL (95% CI: −9.30, −3.52 mg/dL, P < 0.0001; I² = 74%, P < 0.0001) compared with non-soy protein controls. There was no dose–response effect or evidence of publication bias for either outcome. Inspection of the individual trial estimates indicated most trials (∼75%) showed a reduction in LDL cholesterol (range: −0.77 to −58.60 mg/dL), although only a minority of these were individually statistically significant. Conclusions: Soy protein significantly reduced LDL cholesterol by approximately 3–4% in adults. Our data support the advice given to the general public internationally to increase plant protein intake. This trial was registered at clinicaltrials.gov as NCT03468127.

Dietary Proteins and Protein Sources and Risk of Death: The Kuopio Ischaemic Heart Disease Risk Factor Study


Significance: Higher animal to plant protein intake ratios were associated with increased mortality risk in this prospective, population-based study.

Background: Previous studies investigating protein intake in relation to mortality have provided conflicting results. Objective: We investigated the associations of dietary protein and protein sources with risk of disease death in the prospective, population-based Kuopio Ischaemic Heart Disease Risk Factor Study. Methods: The study population consisted of 2641 Finnish men, aged 42–60 y at baseline in 1984–1989. We estimated protein intakes with 4-d dietary records at baseline and collected data on disease deaths from the national Causes of Death Register. Cox proportional hazards regression models were used to estimate HRs and 95% CIs. Results: During the average follow-up of 22.3 y, we observed 1225 deaths due to disease. Higher intakes of total protein and animal protein had borderline statistically significant associations with increased mortality risk: multivariable-adjusted HR (95% CI) in the highest compared with the lowest quartile for total protein intake = 1.17 (0.99, 1.39; P-trend across quartiles = 0.07) and for animal protein intake = 1.13 (0.95, 1.35; P-trend = 0.04). Higher animal-to-plant protein ratio
April 2019 Nutrition Briefs

Strategy to Reduce Daily Exposure to Postprandial Hyperglycemia.

Our purpose was to investigate whether restricting carbohydrates at breakfast would be a simple and feasible strategy to reduce daily exposure to postprandial hyperglycemia. Design: Adults with physician-diagnosed type 2 diabetes (n = 23; mean ± SD age: 59 ± 11 y; glycated hemoglobin: 6.7% ± 0.6%; body mass index (kg/m2): 31 ± 7) completed two 24-h isocaloric intervention periods in a random order. Participants consumed one of the following breakfasts: 1) a very-low-carbohydrate high-fat breakfast (LCBF; <10% of energy from carbohydrate, 85% of energy from fat, 15% of energy from protein) or 2) a breakfast with dietary guidelines–recommended nutrient profile (GLBF; 55% of energy from carbohydrate, 30% of energy from fat, 15% of energy from protein) or 3) a fatty acid desaturase 1 genotype (when available).

Background: Global dietary recommendations for and cardiovascular effects of linoleic acid, the major dietary omega-6 fatty acid, and its major metabolite, arachidonic acid, remain controversial. To address this uncertainty and inform international recommendations, we evaluated how in vivo circulating and tissue levels of linoleic acid (LA) and arachidonic acid (AA) relate to incident cardiovascular disease (CVD) across multiple international studies. Methods: We performed harmonized, de novo, individual-level analyses in a global consortium of 30 prospective observational studies from 13 countries. Multivariable-adjusted associations of circulating and adipose tissue LA and AA biomarkers with incident total CVD and subtypes (coronary heart disease (CHD), ischemic stroke, cardiovascular mortality) were investigated according to a prespecified analytical plan. Levels of LA and AA, measured as % of total fatty acids, were evaluated linearly according to their interquintile range (i.e., the range between the mid-point of the first and fifth quintiles), and categorically by quintiles. Study-specific results were pooled using inverse-variance weighted meta-analysis. Heterogeneity was explored by age, sex, race, diabetes, statin use, aspirin use, omega-3 levels, and fatty acid desaturase 1 genotype (when available).

Results: In 30 prospective studies with medians of follow-up ranging 2.5 to 31.9 years, 15,198 incident cardiovascular events occurred among 68,659 participants. Higher levels of LA were significantly associated with lower risks of total CVD, cardiovascular mortality, and ischemic stroke, with hazard ratios per interquintile range of 0.93 (95% CI: 0.88-0.99), 0.78 (0.70-0.85), and 0.88 (0.79-0.98), respectively, and nonsignificantly with lower CHD risk (0.94; 0.88-1.00). Relationships were similar for LA evaluated across quintiles. AA levels were not associated with higher risk of cardiovascular outcomes; comparing extreme quintiles, higher levels were associated with lower risk of total CVD (0.92; 0.86-0.99). No consistent heterogeneity by population subgroups was identified in the observed relationships. Conclusions: In pooled global analyses, higher in vivo circulating and tissue levels of LA and possibly AA were associated with lower risk of major cardiovascular events. These results support a favorable role for LA in CVD prevention.

Lipids

Biomarkers of Dietary Omega-6 Fatty Acids and Incident Cardiovascular Disease and Mortality: An Individual-Level Pooled Analysis of 30 Cohort Studies


Significance: An analysis of prospective observational studies from 13 countries found that circulating and tissue levels of linoleic acid were inversely associated with risk of major cardiovascular events.

Carbohydrates

Restricting Carbohydrates at Breakfast Is Sufficient to Reduce 24-Hour Exposure to Postprandial Hyperglycemia and Improve Glycemic Variability


Significance: Carbohydrate restriction at breakfast reduced postprandial hyperglycemia after breakfast and reported levels of hunger before dinner.

Background: The breakfast meal often results in the largest postprandial hyperglycemic excursion in people with type 2 diabetes. Objective: Our purpose was to investigate whether restricting carbohydrates at breakfast would be a simple and feasible strategy to reduce daily exposure to postprandial hyperglycemia. Design: Adults with physician-diagnosed type 2 diabetes (n = 1094) compared with those without disease history (n = 1547) (P-interaction = 0.05 or 0.07, depending on the model). Intakes of fish, eggs, dairy, or plant protein sources were not associated with mortality. Conclusions: Higher ratio of animal to plant protein in diet and higher meat intake were associated with increased mortality risk. Higher total protein intake appeared to be associated with mortality mainly among those with a predisposing disease. This trial was registered at clinicaltrials.gov as NCT03221127.
Nutrition Briefs

Low-Calorie Sweeteners

A Randomized Controlled Trial Contrasting the Effects of 4 Low-Calorie Sweeteners and Sucrose on Body Weight in Adults With Overweight or Obesity


Significance: Low-calorie sweeteners elicit distinct and differing effects on body weight.

Background: Low-calorie sweeteners (LCSs) provide sweetness with little or no energy. However, each LCS's unique chemical structure has potential to elicit different sensory, physiological, and behavioral responses that affect body weight. Objective: The purpose of this trial was to compare the effects of consumption of 4 LCSs and sucrose on body weight, ingestive behaviors, and glucose tolerance over a 12-wk intervention in adults (18–60 y old) with overweight or obesity (body mass index 25–40 kg/m2). Methods: In a parallel-arm design, 154 participants were randomly assigned to consume 1.25–1.75 L of beverage sweetened with sucrose (n = 39), aspartame (n = 30), saccharin (n = 29), sucralose (n = 28), or rebaudioside A (rebA) (n = 28) daily for 12 wk. The beverages contained 400–560 kcal/d (sucrose treatments) or <5 kcal/d (LCS treatments). Anthropometric indexes, energy intake, energy expenditure, appetite, and glucose tolerance were measured at baseline. Body weight was measured every 2 wk with energy intake, expenditure, and appetite assessed every 4 wk. Twenty-four-hour urine collections were completed every 4 wk to determine study compliance via para-aminobenzoic acid excretion. Results: Of the participants enrolled in the trial, 123 completed the 12-wk intervention. Sucrose and saccharin consumption led to increased body weight across the 12-wk intervention (Δweight = +1.85 ± 0.36 kg and +1.18 ± 0.36 kg, respectively; P ≤ 0.02) and did not differ from each other. There was no significant change in body weight with consumption of the other LCS treatments compared with baseline, but change in body weight for sucralose was negative and significantly lower compared with all other LCSs at week 12 (weight difference ≥ 1.37 ± 0.52 kg, P ≤ 0.008). Energy intake decreased with sucralose consumption (P = 0.02) and ingestive frequency was lower for sucralose than for saccharin (P = 0.045). Glucose tolerance was not significantly affected by any of the sweetener treatments. Conclusions: Sucrose and saccharin consumption significantly increase body weight compared with aspartame, rebA, and sucralose, whereas weight change was directionally negative and lower for sucralose compared with saccharin, aspartame, and rebA consumption. LCSs should be categorized as distinct entities because of their differing effects on body weight. This trial was registered at clinicaltrials.gov as NCT02928653.

Bioactives

Application of Blood Concentration Biomarkers in Nutritional Epidemiology: Example of Carotenoid and Tocopherol Intake in Relation to Chronic Disease Risk


Significance: Serum-based intake biomarkers from epidemiologic cohorts may be applied in disease-association studies, without reliance on self-reported dietary data.

Background: Biomarkers provide potential to objectively measure the intake of nutrients and foods, and thereby to strengthen nutritional epidemiology association studies. However, there are only a few established intake biomarkers, mostly based on recovery of nutrients or their metabolites in urine. Blood concentration measures provide a potential biomarker source for many additional nutritional variables, but their use in disease-association studies requires further development. Objective: The aim of this study was to apply recently proposed serum-based carotenoid and tocopherol intake biomarkers and to examine their association with the incidence of major cardiovascular diseases, cancers, and diabetes in a subset of Women’s Health Initiative (WHI) cohorts. Methods: Serum concentrations of α- and β-carotene, lutein plus zeaxanthin (L + Z), and α-tocopherol were routinely measured at baseline in a subset of 5488 enrollees in WHI cohorts. Intake biomarkers for these 4 micronutrients, obtained by combining serum concentrations with participant characteristics, were recently proposed using a 153-woman feeding study within WHI. These biomarker equations are augmented here to include pertinent disease risk factors and are associated with subsequent chronic disease incidence in this WHI subset. Results: HRs for a doubling of micronutrient intake differed only modestly from the null for the outcomes considered. However, somewhat lower risks of specific cardiovascular outcomes, breast cancer, and diabetes were associated with a higher intake of α- and β-carotene, lower risk of diabetes was associated with higher L + Z intake, and elevated risks of certain cardiovascular outcomes were associated with a higher intake of α-tocopherol. These
patterns remained following the exclusion of baseline users of dietary supplements. Conclusions: Concentration biomarkers can be calculated from blood specimens obtained in large epidemiologic cohorts and applied directly in disease-association analyses, without relying on self-reported dietary data. Observed associations between carotenoid and tocopherol biomarkers and chronic disease risk could be usefully evaluated further using stored serum specimens on the entire WHI cohort. This study was registered at www.clinicaltrials.gov as NCT00000611.

**Sodium**

**Urinary Sodium-to-Potassium Ratio and Intake of Sodium and Potassium Among Men and Women From Multiethnic General Populations: The INTERSALT Study**


**Significance:** Urinary sodium to potassium ratios may indicate adherence to WHO sodium intake recommendations, but generally accepted cutoff guidelines need to be established.

The Na/K ratio may be more strongly related to blood pressure and cardiovascular disease than sodium or potassium. The casual urine Na/K ratio can provide prompt on-site feedback, and with repeated measurements, may provide useful individual estimates of the 24-h ratio. The World Health Organization has published guidelines for sodium and potassium intake, but no generally accepted guideline prevails for the Na/K ratio. We used standardized data on 24 h and casual urinary electrolyte excretion obtained from the INTERSALT Study for 10,065 individuals aged 20-59 years from 32 countries (52 populations). Associations between the casual urinary Na/K ratio and the 24-h sodium and potassium excretion of individuals were assessed by correlation and stratification analyses. The mean 24-h sodium and potassium excretions were 156.0 mmol/24 h and 55.2 mmol/24 h, respectively; the mean 24-h urinary Na/K molar ratio was 3.24. Pearson’s correlation coefficients (r) for the casual urinary Na/K ratio with the 24-h sodium and potassium excretions were 0.42 and -0.34, respectively, and these were 0.57 and -0.48 for the 24-h ratio. The urinary Na/K ratio predicted a 24-h urine Na excretion of <85 mmol/day (the WHO recommended guidelines) with a sensitivity of 99.7% and 94.0%, specificity of 39.5% and 48.0%, and positive predictive value of 96.3% and 61.1% at the cutoff point of 1 in 24 h and casual urine Na/K ratios, respectively. A urinary Na/K molar ratio <1 may be a useful indicator for adherence to the WHO recommended levels of sodium and, to a lesser extent, the potassium intake across different populations; however, cutoff points for Na/K ratio may be tuned for localization.

**Microbiome**

**Prebiotics in Irritable Bowel Syndrome and Other Functional Bowel Disorders in Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials**


**Significance:** This systematic review and meta-analysis found no effect of prebiotics on quality of life or gastrointestinal symptoms in patients with irritable bowel syndrome or other functional bowel disorders.

**Background:** Irritable bowel syndrome (IBS) and other functional bowel disorders (FBDs) are prevalent disorders with altered microbiota. Prebiotics positively augment gut microbiota and may offer therapeutic potential. **Objectives:** The aim of this study was to investigate the effect of prebiotics compared with placebo on global response, gastrointestinal symptoms, quality of life (QoL), and gut microbiota, via systematic review and meta-analysis of randomized controlled trials (RCTs) in adults with IBS and other FBDs. **Methods:** Studies were identified using electronic databases, back-searching reference lists, and hand-searching abstracts. RCTs that compared prebiotics to placebo in adults with IBS or other FBDs were included. Two reviewers independently performed screening, data extraction, and bias assessment. Outcome data were synthesized as ORs, weighted mean differences (WMDs) or standardized mean differences (SMDs) with the use of a random-effects model. Subanalyses were performed for type of FBD and dose, type, and duration of prebiotic. **Results:** Searches identified 2332 records, and 11 RCTs were eligible (729 patients). The numbers responding were 52/97 (54%) for prebiotic and 59/94 (63%) for placebo, with no difference between groups (OR: 0.62; 95% CI: 0.07, 5.69; P = 0.67). Similarly, no differences were found for severity of abdominal pain, bloating and flatulence, and QoL score between prebiotics and placebo. However, flatulence severity was improved by prebiotics at doses ≤6 g/d (SMD: -0.35; 95% CI: -0.71, 0.00; P = 0.05) and by non-inulin-type fructan prebiotics (SMD: -0.34; 95% CI: -0.66, -0.01; P = 0.04), while inulin-type fructans worsened flatulence (SMD: 0.85; 95% CI: 0.23, 1.47; P = 0.007). Prebiotics increased absolute abundance of bifidobacteria (WMD: 1.16 log10 copies of the 16S ribosomal RNA gene; 95% CI: 0.06, 2.26; P = 0.04). No studies were at low risk of bias across all bias categories. **Conclusions:** Prebiotics do not improve gastrointestinal symptoms or QoL in patients with IBS or other FBDs, but they do increase bifidobacteria. Variations in prebiotic type and dose impacted symptom improvement or exacerbation. This review was registered at PROSPERO as CRD42017074072.
Personalized Nutrition

Weight Loss at Your Fingertips: Personalized Nutrition With Fasting Glucose and Insulin Using a Novel Statistical Approach


**Significance:** A statistical approach utilizing pre-treatment fasting plasma glucose and fasting insulin to predict treatment effect of diet on weight loss is presented.

**Background/Objectives:** Precision medicine is changing the way people are diagnosed and treated into a more personalized approach. Using a novel statistical approach, we demonstrate how two diets cause differential weight loss depending on pre-treatment fasting plasma glucose (FPG) and fasting insulin (FI) levels. **Subjects/Methods:** One hundred and eighty-one overweight people with increased waist circumference were randomly assigned to receive an ad libitum New Nordic Diet (NND) high in dietary fiber and whole grain or an Average Danish (Western) Diet (ADD) for 26 weeks. All foods were provided free of charge. Body weight was measured throughout the study and blood was drawn before randomization from where FPG and FI were analyzed. Weight was described by linear mixed models including biomarker (FPG or FI) diet group interactions. Individualized predictions were estimated as contrasts of intercepts and slopes of pre-treatment biomarkers. **Results:** Every mmol/L increase in baseline FPG predicted a between-diet difference of 3.00 (1.18;4.83, n = 181, P = 0.001) kg larger weight loss from choosing NND over ADD. For instance, a baseline FPG level of 4.7 mmol/L would lead to an average of 1.42 kg larger weight loss on NND vs. ADD (above 0.41 kg with 95% certainty), whereas the average effect size would be 8.33 kg (above 5.50 kg with 95% certainty) among subjects with FPG level of 7.0 mmol/L. Among individuals with FPG <5.6 mmol/L, each pmol/L lower baseline FI predicted a 0.039 (95% CI 0.017;0.061, n = 143, P < 0.001) kg larger weight loss from choosing NND over ADD. **Conclusions:** Use of pre-treatment FPG and FI led to truly individualized predictions of treatment effect of introducing more fiber and whole grain in the diet on weight loss, ranging from almost no effect to losing >8 kg. These findings suggest that this novel statistical approach has great potential when re-evaluating data from existing randomized controlled trials.