**Dietary Patterns**

**Portfolio Dietary Pattern and Cardiovascular Disease: A Systematic Review and Meta-Analysis of Controlled Trials**


**Significance:** This systematic review and meta-analysis found that the Portfolio dietary pattern improves cardiometabolic risk factors and 10-year coronary heart disease risk.

**Background:** The evidence for the Portfolio dietary pattern, a plant-based dietary pattern that combines recognized cholesterol-lowering foods (nuts, plant protein, viscous fibre, plant sterols), has not been summarized. Objective: To update the European Association for the Study of Diabetes clinical practice guidelines for nutrition therapy, we conducted a systematic review and meta-analysis of controlled trials using GRADE of the effect of the Portfolio dietary pattern on the primary therapeutic lipid target for cardiovascular disease prevention, low-density lipoprotein cholesterol (LDL-C), and other established cardiometabolic risk factors. Methods: We searched MEDLINE, EMBASE, and The Cochrane Library through April 19, 2018. We included controlled trials ≥ 3-weeks assessing the effect of the Portfolio dietary pattern on cardiometabolic risk factors compared with an energy-matched control diet free of Portfolio dietary pattern components. Two independent reviewers extracted data and assessed risk of bias. The primary outcome was LDL-C. Data were pooled using the generic inverse-variance method and expressed as mean differences (MDs) with 95% confidence intervals (CIs). Heterogeneity was assessed (Cochran Q statistic) and quantified (I²-statistic). GRADE assessed the certainty of the evidence. Results: Eligibility criteria were met by 7 trial comparisons in 439 participants with hyperlipidemia, in which the Portfolio dietary pattern was given on a background of a National Cholesterol Education Program (NCEP) Step II diet. The combination of a portfolio dietary pattern and NCEP Step II diet significantly reduced the primary outcome LDL-C by ~17% (MD, -0.73mmol/L, [95% CI, -0.89 to -0.56 mmol/L]) as well as non-high-density lipoprotein cholesterol, apolipoprotein B, total cholesterol, triglycerides, systolic and diastolic blood pressure, C-reactive protein, and estimated 10-year coronary heart disease (CHD) risk, compared with an NCEP Step 2 diet alone (P<0.05). There was no effect on high-density lipoprotein cholesterol or body weight. The certainty of the evidence was high for LDL-cholesterol and most lipid outcomes and moderate for all others outcomes. Conclusions: Current evidence demonstrates that the Portfolio dietary pattern leads to clinically meaningful improvements in LDL-C as well as other established cardiometabolic risk factors and estimated 10-year CHD risk.

**A Mediterranean-Style Eating Pattern with Lean, Unprocessed Red Meat has Cardiometabolic Benefits for Adults who are Overweight or Obese in a Randomized, Crossover, Controlled Feeding Trial**


**Significance:** A Mediterranean diet pattern that includes lean, unprocessed red meat can be used to achieve improvements in cardiometabolic risk factors in overweight adults.

**Background:** A Mediterranean-style eating pattern (Mediterranean Pattern) is often described as being low in red meat. Research shows that lean, unprocessed red meat can be incorporated into healthy eating patterns to improve cardiometabolic disease (CMD) risk factors. Objective: We assessed the effects of consuming different amounts of lean, unprocessed red meat in a Mediterranean Pattern on CMD risk factors. We hypothesized that consuming a Mediterranean Pattern would improve CMD risk factors and that red meat intake would not influence these improvements. Design: In an investigator-blinded, randomized, crossover, controlled feeding trial, 41
subjects [mean ± SD age: 46 ± 2 y; mean ± SD body mass index (kg/m2): 30.5 ± 0.6] were provided with a Mediterranean Pattern for two 5-wk interventions separated by 4 wk of self-selected eating. The Mediterranean Patterns contained ~500 g [typical US intake (Med-Red)] and ~200 g [commonly recommended intake in heart-healthy eating patterns (Med-Control)] of lean, unprocessed beef or pork per week. Red meat intake was compensated by poultry and other protein-rich foods. Baseline and postintervention outcomes included fasting blood pressure, serum lipids, lipoproteins, glucose, insulin, and ambulatory blood pressure. The presented results were adjusted for age, sex, and body mass at each time point (P < 0.05). RESULTS: Total cholesterol decreased, but greater reductions occurred with Med-Red than with Med-Control [-0.4 ± 0.1 and -0.2 ± 0.1 mmol/L, respectively, intervention × time = 0.045]. Low-density lipoprotein decreased with Med-Red but was unchanged with Med-Control [-0.3 ± 0.1 and -0.1 ± 0.1 mmol/L, respectively, intervention × time = 0.038], whereas high-density lipoprotein (HDL) concentrations decreased nondifferentially [-0.1 ± 0.0 mmol/L]. Triglycerides, total cholesterol:HDL, glucose, and insulin did not change with either Med-Red or Med-Control. All blood pressure parameters improved, except during sleep, independent of the red meat intake amount. Conclusions: Adults who are overweight or moderately obese may improve multiple cardiometabolic disease risk factors by adopting a Mediterranean-style eating pattern with or without reductions in red meat intake when red meats are lean and unprocessed. This trial was registered at clinicaltrials.gov as NCT02573129.

Total Usual Nutrient Intakes of US Children (Under 48 Months): Findings from the Feeding Infants and Toddlers Study (FITS) 2016

Significance: This analysis identifies specific nutritional gaps and excesses in the usual intakes of infants and toddlers in the US.

Background: The US Dietary Guidelines will expand in 2020 to include infants and toddlers. Understanding current dietary intakes is critical to inform policy. OBJECTIVE: The purpose of this analysis was to examine the usual total nutrient intakes from diet and supplements among US children. METHODS: The Feeding Infants and Toddlers Study 2016 is a national cross-sectional study of children aged <48 mo (n = 3235): younger infants (birth to 5.9 mo), older infants (6-11.9 mo), toddlers (12-23.9 mo), younger preschoolers (24-36.9 mo), and older preschoolers (36-47.9 mo) based on the use of a 24-h dietary recall. A second 24-h recall was collected from a representative subsample (n = 799). Energy, total nutrient intake distributions, and compliance with Dietary Reference Intakes were estimated with the use of the National Cancer Institute method. RESULTS: Dietary supplement use was 15-23% among infants and toddlers and 35-45% among preschoolers. Dietary intakes of infants were adequate, with mean intakes exceeding Adequate Intake for all nutrients except vitamins D and E. Iron intakes fell below the Estimated Average Requirement for older infants (18%). We found that 31-33% of children aged 12-47.9 mo had low percentage of energy from total fat, and >60% of children aged 24-47.9 mo exceeded the saturated fat guidelines. The likelihood of nutrient inadequacy for many nutrients was higher for toddlers: 3.2% and 2.5% greater than the Adequate Intake for fiber and potassium and 76% and 52% less than the Estimated Average Requirement for vitamins D and E, respectively. These patterns continued through older ages. Intakes exceeded the Tolerable Upper Intake Level of sodium, retinol, and zinc across most age groups. CONCLUSIONS: Dietary intakes of US infants are largely nutritionally adequate; concern exists over iron intakes in those aged 6-11.9 mo. For toddlers and preschoolers, high intake of sodium and low intakes of potassium, fiber, and vitamin D and, for preschoolers, excess saturated fat are of concern. Excess retinol, zinc, and folic acid was noted across most ages, especially among supplement users.

Protein:

Protein Intake Trends and Conformity with the Dietary Reference Intakes in the United States: Analysis of the National Health and Nutrition Examination Survey, 2001-2014

Significance: The majority of the US population protein intake exceeds minimum protein intake recommendations, and protein as a percentage of total energy intake is not consumed in excess.

Background: Systematic analysis of dietary protein intake may identify demographic groups within the American population that are not meeting the Dietary Reference Intakes (DRIs). Objective: This cross-sectional study analyzed protein intake trends (2001-2014) and evaluated recent conformity to the DRIs (2011-2014) according to age, sex, and race or ethnicity in the US population. Design: Protein intakes and trends during 2-y cycles of NHANES 2001-2014 (n = 57,980; ≥2 y old) were calculated as absolute (grams per day) and relative [grams per kilogram of ideal body weight (IBW) per day] intakes and as a percentage of total energy. Sex and race or ethnicity [Asian, Hispanic, non-Hispanic black (NHb), and non-Hispanic white (NHW)] differences were determined for protein intake and percentage of the population below the Estimated Average Requirement (EAR) and Recommended Dietary Allowance, and above and below the Acceptable Macronutrient Distribution Range (AMDR). Results: Usual protein intakes (mean ± SE) averaged from 55.3 ± 0.9 (children aged 2-3 y) to 88.2 ± 1.1 g/d (adults aged 19-30 y).
Protein comprised 14-16% of total energy intakes. Relative protein intakes averaged from 1.10 ± 0.01 (adults aged ≥71 y) to 3.63 ± 0.07 g · kg IBW⁻¹ · d⁻¹ (children aged 2-3 y), and were above the EAR in all demographic groups. Asian and Hispanic populations aged >19 y consumed more relative protein (1.32 ± 0.02 and 1.32 ± 0.02 g · kg IBW⁻¹ · d⁻¹, respectively) than did NHB and NHW (1.18 ± 0.01 g · kg IBW⁻¹ · d⁻¹). Relative protein intakes did not differ by race or ethnicity in the 2-18 y population. Adolescent (aged 14-18 y) females and older (aged ≥71 y) NHB men had the largest population percentages below the EAR (11% and 13%, respectively); <1% of any demographic group had intakes above the AMDR. Conclusions: The majority of the US population exceeds minimum recommendations for protein intake. Protein intake remains well below the upper end of the AMDR, indicating that protein intake, as a percentage of energy intake, is not excessive in the American diet. This trial was registered at www.isrctn.com as ISRCTN76534484.

Leucine, Not Total Protein, Content of a Supplement Is the Primary Determinant of Muscle Protein Anabolic Responses in Healthy Older Women


Significance: This study suggests that leucine may stimulate skeletal muscle anabolism and attenuate muscle loss in older women.

Background: Older adults show a blunted muscle protein synthesis (MPS) response to postprandial hyperaminoacidemia relative to younger adults. Evidence suggests that this anabolic resistance can be overcome by consuming greater quantities of leucine. Objective: The purpose of this trial was to determine whether the addition of leucine to a smaller dose (10 g) of milk proteins would, when compared with a larger dose (25 g) of whey protein isolate (WPI), result in similar increases in acute (hourly) and integrated (daily) myofibrillar protein synthesis (myoPS). Methods: Healthy older (mean ± SD age: 69 ± 1 y) women (n = 11/group) were randomly assigned with the use of a single-blind, parallel-group design to twice-daily consumption of either WPI [25 g WPI (3 g l-leucine)] or leucine (LEU; 10 g milk protein with 3 g total l-leucine) for 6 d. Participants performed unilateral resistance exercise to allow assessment of the impact of the supplement alone and with resistance exercise. We determined acute (13C6-phenylalanine) and integrated [using deuterated water (D2O)] rates of myoPS in the fasting (acute), basal (integrated), nonexercised, and exercised states. Results: Acute myoPS increased in both legs in response to LEU (fed: 45%; fed+exercise: 71%; P < 0.001) compared with fasting; the increase was greater with LEU than with WPI in the exercised leg (46%; P = 0.04) but not in the rested leg (P = 0.07). The acute myoPS response was greater in the exercised leg than in the rested leg for both WPI (63%) and LEU (58%) (P < 0.001). Integrated myoPS increased with WPI and LEU in the exercised leg (both 9%; P < 0.001) during supplementation, and with WPI (3%; P = 0.02) but not LEU (2%, P = 0.1) in the rested leg compared with the basal state. Conclusions: A lower-protein (10 compared with 25 g/dose), leucine-matched beverage induced similar increases in acute and integrated myoPS in healthy older women. Lower-protein supplements with added leucine may represent an advantageous approach in older adults to maintain skeletal muscle anabolic sensitivity and attenuate muscle loss; however, further work is needed using longer-term interventions to substantiate these findings. This trial was registered at www.clinicaltrials.gov as NCT02282566.

Carbohydrates:

Recommendations for Characterization and Reporting of Dietary Fibers in Nutrition Research


Significance: This paper describes the factors that affect dietary fiber functionality and provides specific recommendations for characterizing and reporting dietary fibers in nutrition research.

Dietary fiber (DF) comprises a wide range of naturally occurring and modified materials with substantial variations in physical and chemical properties and potential physiologic effects. Although nutrition studies testing the effects of DF usually provide extensive detail on the physiologic responses, many still fail to adequately report the type and properties of the DF itself. This weakens the ability to directly replicate and compare studies and to establish structure-function relations. We outline the factors that affect DF functionality and provide 4 overarching recommendations for the characterization and reporting of DF preparations and DF-containing foods in nutrition research. These relate to 1) undertaking characterization methods that reflect the study hypothesis; 2) adequate reporting of DF source, quantity, and composition; 3) measurement of DF rheological properties; and 4) estimation of the DF fermentation rate and extent. Importantly, the food matrix of the test products should also be considered, because this can influence DF functionality and hence the apparent DF efficacy for health-relevant outcomes. Finally, we point out differences in DF functionality to be considered in acute and longer-term trials, the need to design the control treatment according to the research question, and the importance of reporting the amount and type of DF in the background diet.
Micronutrients:

Effects of Vitamin D Supplementation on Markers for Cardiovascular Disease and Type 2 Diabetes: An Individual Participant Data Meta-Analysis of Randomized Controlled Trials


Significance: This meta-analysis found no effect of vitamin D supplementation on blood pressure and HbA1c, and a lowering effect on LDL cholesterol.

Background: Evidence from randomized controlled trials (RCTs) for the causal role of vitamin D on noncommunicable disease outcomes is inconclusive. Objective: The aim of this study was to investigate whether there are beneficial or harmful effects of cholecalciferol (vitamin D3) supplementation according to subgroups of remeasured serum 25-hydroxyvitamin D [25(OH)D] on cardiovascular and glucometabolic surrogate markers with the use of individual participant data (IPD) meta-analysis of RCTs. Design: Twelve RCTs (16 wk to 1 y of follow-up) were included. For standardization, 25(OH)D concentrations for all participants (n = 2994) at baseline and postintervention were re-measured in bio-banked serum samples with the use of a certified liquid chromatography-tandem mass spectrometry method traceable to a reference measurement procedure. IPD-meta-analyses were performed according to subgroups of remeasured 25(OH)D. Main outcomes were blood pressure and glycated hemoglobin (HbA1c). Secondary outcomes were LDL, HDL, and total cholesterol and triglycerides; parathyroid hormone (PTH); fasting glucose, insulin, and C-peptide; and 2-h glucose. In secondary analyses, other potential effect modifiers were studied. Results: Remeasurement of 25(OH)D resulted in a lower mean 25(OH)D concentration in 10 of 12 RCTs. Vitamin D supplementation had no effect on the main outcomes of blood pressure and HbA1c. Supplementation resulted in 10-20% lower PTH concentrations, irrespective of the 25(OH)D subgroups. The subgroup analyses according to achieved 25(OH)D concentrations showed a significant decrease in LDL-cholesterol concentrations after vitamin D supplementation in 25(OH)D subgroups with <75, <100, and <125 nmol of -0.10 mmol/L (95% CI: -0.20, -0.00 mmol/L), -0.10 mmol/L (95% CI: -0.18, -0.02 mmol/L), and -0.07 mmol/L (95% CI: -0.14, -0.00 mmol/L), respectively. Patient features that modified the treatment effect could not be identified. Conclusions: For the main outcomes of blood pressure and HbA1c, the data support no benefit for vitamin D supplementation. For the secondary outcomes, in addition to its effect on PTH, we observed indications for a beneficial effect of vitamin D supplementation only on LDL cholesterol, which warrants further investigation. This trial was registered at www.clinicaltrials.gov as NCT02551835.

Bioactives:

Polyphenol Exposure and Risk of Type 2 Diabetes: Dose-Response Meta-Analyses and Systematic Review of Prospective Cohort Studies


Significance: This study adds to the evidence showing that diets rich in polyphenols, and particularly flavonoids, may play a role in the prevention of type 2 diabetes.

Background: Type 2 diabetes is characterized by impaired glucose metabolism. Bioactive compounds in fruits and vegetables such as polyphenols have been suggested to influence glucose metabolism. Objective: The aim of the current study was to systematically review the literature and conduct dose-response meta-analyses to summarize evidence of polyphenol exposure in association with type 2 diabetes. Design: Prospective epidemiologic studies published before January 2018 were searched through 2 databases. Log-transformed multivariable adjusted hazard and odds ratios were combined in a random-effects model. Meta-analyses comparing extreme quantiles of polyphenol exposure were further explored with the use of linear and nonlinear dose-response meta-analyses. Results: Eighteen studies investigated the association between polyphenols (51 different compounds in total) and type 2 diabetes. A comparison of extreme quantiles revealed inverse associations for intakes of polyphenols (HR: 0.56; 95% CI: 0.34, 0.93), flavonoids (HR: 0.88; 95% CI: 0.81, 0.96), flavonols (HR: 0.92; 95% CI: 0.85, 0.98), flavan-3-ols (HR: 0.89; 95% CI: 0.81, 0.99), catechins (HR: 0.86; 95% CI: 0.75, 0.97), anthocyanidins (HR: 0.86; 95% CI: 0.81, 0.91), isoflavones (HR: 0.92; 0.86, 0.97), daidzein (HR: 0.89; 95% CI: 0.83, 0.95), genistein (HR: 0.92; 95% CI: 0.86, 0.99), and stilbenes (HR: 0.44; 95% CI: 0.26, 0.72), and biomarkers of daidzein (HR: 0.81; 95% CI: 0.66, 0.99) and genistein (HR: 0.79; 95% CI: 0.62, 0.99). In the dose-response meta-analysis, nonlinear associations were observed for intakes of polyphenols, flavonoids, flavanones, anthocyanidins, anthocyanins, and biomarkers of genistein. A linear dose-response association was observed for phenolic acids. Conclusions: This study adds to the evidence showing that diets rich in polyphenols, and particularly flavonoids, play a role in the prevention of type 2 diabetes. For most associations evidence for nonlinearity was found, suggesting a recommendable amount of intake associated with the lowest risk of type 2 diabetes. Therefore, future studies are warranted in which nonlinear associations are further explored.
Dietary Lipids:

**Effects of Walnut Consumption on Blood Lipids and Other Cardiovascular Risk Factors: An Updated Meta-Analysis and Systematic Review of Controlled Trials**


**Significance:** Incorporating walnuts into the diet may improve blood lipid profile without negatively affecting weight or blood pressure.

**Background:** Intervention studies suggest that incorporating walnuts into the diet may improve blood lipids without promoting weight gain. **Objective:** We conducted a systematic review and meta-analysis of controlled trials evaluating the effects of walnut consumption on blood lipids and other cardiovascular risk factors. **Design:** We conducted a comprehensive search of PubMed and EMBASE databases (from database inception to January 2018) of clinical trials comparing walnut-enriched diets with control diets. We performed random-effects meta-analyses comparing walnut-enriched and control diets for changes in pre-post intervention in blood lipids (mmol/L), apolipoproteins (mg/dL), body weight (kg), and blood pressure (mm Hg). **Results:** Twenty-six clinical trials with a total of 1059 participants were included. The following weighted mean differences (WMDs) in reductions were obtained for walnut-enriched diets compared with control groups: -6.99 mg/dL (95% CI: -9.39, -4.58 mg/dL; P < 0.001) (3.25% greater reduction) for total blood cholesterol (TC) and -5.51 mg/dL (95% CI: -7.72, -3.29 mg/dL; P < 0.001) (3.73% greater reduction) for low-density lipoprotein (LDL) cholesterol. Triglyceride concentrations were also reduced in walnut-enriched diets compared with control [WMD = -4.69 (95% CI: -8.93, -0.45); P = 0.03; 5.52% greater reduction]. More pronounced reductions in blood lipids were observed when walnut interventions were compared with American and Western diets [WMD for TC = -12.30 (95% CI: -23.17, -1.43) and for LDL = -8.28 (95% CI: -13.04, -3.51); P < 0.001]. Apolipoprotein B (mg/dL) was also reduced significantly more on walnut-enriched diets compared with control groups [WMD = -3.74 (95% CI: -6.51, -0.97); P = 0.008] and a trend towards a reduction was observed for apolipoprotein A [WMD = -2.91 (95% CI: -5.98, 0.08); P = 0.057]. Walnut-enriched diets did not lead to significant differences in weight change (kg) compared with control diets [WMD = -0.12 (95% CI: -2.12, 1.88); P = 0.90], systolic blood pressure (mm Hg) [WMD = -0.72 (95% CI: -2.75, 1.30); P = 0.48], or diastolic blood pressure (mm Hg) [WMD = -0.10 (95% CI: -1.49, 1.30); P = 0.88]. **Conclusions:** Incorporating walnuts into the diet improved blood lipid profile without adversely affecting body weight or blood pressure.

**Systematic Review and Meta-Analysis of Controlled Intervention Studies on the Effectiveness of Long-Chain Omega-3 Fatty Acids in Patients with Nonalcoholic Fatty Liver Disease**


**Significance:** Supplementation with omega-3 long-chain polyunsaturated fatty acids improves metabolic and liver-related outcomes in patients with nonalcoholic fatty liver disease.

**Context:** Treatment options for nonalcoholic fatty liver disease (NAFLD) are needed. **Objective:** The aim of this review was to systematically assess the effects of omega-3 long-chain polyunsaturated fatty acids (n-3 LC-PUFAs), particularly eicosapentaenoic acid and docosahexaenoic acid, on liver-related and metabolic outcomes in adult and pediatric patients with NAFLD. **Data Sources:** The online information service ProQuest Dialog was used to search 8 literature databases. **Study Selection:** Controlled intervention studies in which the independent effects of n-3 LC-PUFAs could be isolated were eligible for inclusion. **Data Extraction:** The 18 unique studies that met the criteria for inclusion were divided into 2 sets, and data transcriptions and study quality assessments were conducted in duplicate. Each effect size was expressed as the weighted mean difference and 95% CI, using a random-effects model and the inverse of the variance as a weighting factor. **Results:** Based on the meta-analyses, supplementation with n-3 LC-PUFAs resulted in statistically significant improvements in 6 of 13 metabolic risk factors, in levels of 2 of 3 liver enzymes, in liver fat content (assessed via magnetic resonance imaging/spectroscopy), and in steatosis score (assessed via ultrasonography). Histological measures of disease [which were assessed only in patients with nonalcoholic steatohepatitis (NASH)] were unaffected by n-3 LC-PUFA supplementation. **Conclusions:** Omega-3 LC-PUFAs are useful in the dietary management of patients with NAFLD. Additional trials are needed to better understand the effects of n-3 LC-PUFAs on histological outcomes in patients with NASH. **Systematic Review Registration:** PROSPERO CRD42017055951.