Dietary Approaches to Stop Hypertension (DASH) Diet and Blood Pressure Reduction in Adults With and Without Hypertension: A Systematic Review and Meta-Analysis of Randomized Controlled Trials


Significance: The adoption of the DASH diet reduced blood pressure (BP) in adults with and without hypertension, although higher daily sodium intake and younger age enhanced its BP-lowering effects.

The Dietary Approaches to Stop Hypertension (DASH) diet is recognized as an effective dietary intervention to reduce blood pressure (BP). However, among randomized controlled trials (RCTs) investigating the DASH diet-mediated BP reduction, there are significant methodological and clinical differences. The purpose of this study was to comprehensively assess the DASH diet effect on BP in adults with and without hypertension, accounting for underlying methodological and clinical confounders. We systematically searched Medline and the Cochrane Collaboration Library databases and identified 30 RCTs (n = 5545 participants) that investigated the BP effects of the DASH diet compared with a control diet in hypertensive and nonhypertensive adults. Both random-effects and fixed-effect models were used to calculate the mean attained systolic BP (SBP) and diastolic BP (DBP) differences during follow-up. Subgroup and meta-regression analyses were also conducted. Compared with a control diet, the DASH diet reduced both SBP and DBP (difference in means: −3.2 mm Hg; 95% CI: −4.2, −2.3 mm Hg; P < 0.001, respectively). Hypertension status did not modify the effect on BP reduction. The DASH diet compared with a control diet reduced SBP levels to a higher extent in trials with sodium intake >2400 mg/d than in trials with sodium intake ≤2400 mg/d, whereas both SBP and DBP were reduced more in trials with mean age <50 y than in trials of older participants. The quality of evidence was rated as moderate for both outcomes according to the Grading of Recommendations, Assessment, Development, and Evaluation approach. The adoption of the DASH diet was accompanied by significant BP reduction in adults with and without hypertension, although higher daily sodium intake and younger age enhanced the BP-lowering effect of the intervention.

Protein

Protein Intake Is More Stable Than Carbohydrate or Fat Intake Across Various US Demographic Groups and International Populations


Significance: Protein intake across international populations, regardless of demographic and lifestyle factors, was consistently ~16% of total energy, suggesting biological control mechanism(s) tightly regulate intake.

Background: The optimal macronutrient composition of the diet is controversial and many adults attempt to regulate the intake of specific macronutrients for various health-related reasons. Objective: The objective was to compare stability and ranges of intakes of different macronutrients across diverse adult populations in the USA and globally. Methods: US dietary intake data from NHANES 2009-2014 were used to determine macronutrient intake as a percentage of total energy intake. Variability in
Protein intake of the US population and multiple international populations, regardless of demographic and lifestyle factors, was consistently 16% of total energy, suggesting biological control mechanisms(s) tightly regulate protein intake and, consequently, influence intake of other macronutrients and food constituents. Substantial differences in intake of the other macronutrients observed in US and international populations had little influence on protein intake. This trial was registered at the ISRCTN registry as ISRCTN46157745 (https://www.isrctn.com/ISRCTN46157745).

**The Role of Protein Intake and Its Timing on Body Composition and Muscle Function in Healthy Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials**


**Significance:** Protein supplementation increased lean body mass but not handgrip or leg press muscle strength.

**Background:** Increased protein intake has been suggested to improve gains in muscle mass and strength in adults. Furthermore, the timing of protein intake has been discussed as a margin of opportunity for improved prevention measures. **Objective:** This systematic review investigated the effect of protein supplementation on body composition and muscle function (strength and synthesis) in healthy adults, with an emphasis on the timing of protein intake. **Methods:** Randomized controlled trials were identified using PubMed, Web of Science, CINAHL, and Embase, up to March 2019. For meta-analyses, data on lean body mass (LBM), handgrip strength, and leg press strength were pooled by age group (mean age 18-55 or >55 y) and timing of protein intake. The quality of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluations approach. Data from 65 studies with 2907 participants (1514 men and 1380 women, 13 unknown sex) were included in the review. Twenty-six, 8, and 24 studies were used for meta-analysis on LBM, handgrip strength, and leg press strength, respectively. The protein supplementation was effective in improving (mean difference; 95% CI) LBM in adults (0.62 kg; 0.36, 0.88) and older adults (0.46 kg; 0.23, 0.70), but not handgrip strength (older adults: 0.26 kg; -0.51, 1.04) and leg press strength (adults: 5.80 kg; -0.33, 11.93; older adults: 1.97 kg; -2.78, 6.72). Sensitivity analyses removing studies without exercise training had no impact on the outcomes. **Results:** Data regarding muscle synthesis were scarce and inconclusive. Subgroup analyses showed no beneficial effect of a specific timing of protein intake on LBM, handgrip strength, and leg press strength. **Conclusions:** Overall, the results support the positive impact of protein supplementation on LBM of adults and older adults, independently of intake timing. Effects on muscle strength and synthesis are less clear and need further investigation. This systematic review was registered on PROSPERO as CRD42019126742.

**Lipids**

**A Review of Lipidomics of Cardiovascular Disease Highlights the Importance of Isolating Lipoproteins**


**Significance:** This review introduces lipidomic techniques to investigate mechanisms of cardiovascular disease, and summarizes the findings of 16 cohort studies using lipidomics to examine the association of lipids with CVD.

Cutting-edge lipidomic profiling measures hundreds or even thousands of lipids in plasma and is increasingly used to investigate mechanisms of cardiovascular disease (CVD). In this review, we introduce lipidomic techniques, describe distributions of lipids across lipoproteins, and summarize findings on the association of lipids with CVD based on lipidomics. The main findings of 16 cohort studies were that, independent of total and high-density lipoprotein cholesterol (HDL-c), ceramides (d18:1/16:0, d18:1/18:0, and d18:1/24:1) and phosphatidylcholines (PCs) containing saturated and monounsaturated fatty acyl chains are positively associated with risks of CVD outcomes, while PCs containing polyunsaturated fatty acyl chains (PUFA) are inversely associated with risks of CVD outcomes. Lysophosphatidylcholines (LPCs) may be positively associated with risks of CVD outcomes. Interestingly, the distributions of the identified lipids vary across lipoproteins: LPCs are primarily contained in HDLs, ceramides are mainly contained in low-density lipoproteins (LDLs), and PCs are distributed in both HDLs and LDLs. Thus, the potential mechanism behind previous findings may be related to the effect of the identified lipids on the biological functions of HDLs and LDLs. Only eight studies on the lipidomics of HDL and non-HDL particles and CVD outcomes have been conducted, which showed that higher triglycerides (TAGs), lower PUFA, lower phospholipids, and lower sphingomyelin content in HDLs might be associated with a higher risk of coronary heart disease (CHD). However, the generalizability of these studies is a major concern, given that
they used case-control or cross-sectional designs in hospital settings, included a very small number of participants, and did not correct for multiple testing or adjust for blood lipids such as HDL-c, low-density lipoprotein cholesterol (LDL-c), or TAGs. Overall, findings from the literature highlight the importance of research on lipidomics of lipoproteins to enhance our understanding of the mechanism of the association between the identified lipids and the risk of CVD and allow the identification of novel lipid biomarkers in HDLs and LDLs, independent of HDL-c and LDL-c. Lipidomic techniques show the feasibility of this exciting research direction, and the lack of high-quality epidemiological studies warrants well-designed prospective cohort studies.

### Carbohydrates

**Very Low and Higher Carbohydrate Diets Promote Differential Appetite Responses in Adults with Type 2 Diabetes: A Randomized Trial**


**Significance:** In adults with overweight/obesity and type 2 diabetes, an energy-restricted higher carbohydrate diet resulted in greater “daily overall” fullness and reduced prospective consumption versus an energy-matched very-low carbohydrate diet.

**Background:** Effects of very low carbohydrate (VLC) diets on appetite response in individuals with type 2 diabetes remain unclear. **Objective:** A secondary analysis was conducted to determine appetite responses to an energy-restricted [30% of energy (%E) deficit] very low carbohydrate (VLC) diet compared with a higher carbohydrate (HC) diet in adults who were overweight or obese with type 2 diabetes. **Methods:** Forty-four men and 40 women (mean ± SD, age: 58.7 ± 6.6 y; weight: 100.4 ± 15.5 kg; BMI: 34.5 ± 4.1 kg/m²; glycated hemoglobin: 7.3 ± 1.0%; duration of diabetes: 6.7 ± 5.6 y) were randomly assigned to diets categorized as VLC [14%E carbohydrate (<50 g/d), 28%E protein, 58%E fat (<10%E saturated fat)], or energy-matched HC [53%E carbohydrate, 17%E protein, 30%E fat (<10%E saturated fat)] combined with progressive multicomponent exercise (60 min; 3 d/wk). Body weight, average weekly “daily fasting” and “daily overall” appetite perceptions (hunger, fullness, prospective consumption, and desire to eat) were assessed at baseline and after 4 and 16 wk. Changes between diets over time were assessed using repeated measures ANOVA. **Results:** Significant decreases in body weight did not differ between groups (VLC: -11.0 ± 5.4 kg/16 wk compared with HC: -10.1 ± 4.3 kg/16 wk, P = 0.40). Compared with HC, VLC had greater decreases in “daily overall” ratings of fullness (P time × diet < 0.01), such that scores were higher in HC at Week 4 (VLC:48 ± 3 vs HC:56 ± 3 mm, P = 0.001) and 16 (VLC:51 ± 2 vs HC:57 ± 3 mm, P = 0.019). Compared with HC, VLC had greater increases in prospective consumption ratings (P time × diet = 0.03), such that scores were lower in HC at Week 4 (VLC:33 ± 2 vs HC:28 ± 2 mm, P = 0.008), but not at Week 16 (VLC:33 ± 2 vs HC 31 ± 2 mm, P = 0.289). **Conclusions:** In the context of energy restriction, both HC and VLC energy-matched diets promoted comparable effects on fasting perceptions of appetite, but the HC diet resulted in greater “daily overall” fullness and reduced prospective consumption. Further research is required to evaluate the effects of ad libitum diets differing in amounts of carbohydrate on appetite response in populations with type 2 diabetes. This trial was registered at www.anzctr.org.au as ACTRN12612000369820.

**The Association Between Carbohydrate Quality and Nutrient Adequacy in Australian Adults**


**Significance:** Of the carbohydrate quality indicators examined, intake of high-GI carbohydrates was the strongest predictor of nutrient adequacy in Australian adults.

**Background/Methods:** To examine the association between various carbohydrate quality indicators and nutrient adequacy in Australian adults. **Subjects/Methods:** Dietary data from adult participants of the 2011-2012 Australian Health Survey (weighted n = 6150) who had completed two 24 h recalls were analyzed. Glycaemic indices (GI) of foods were estimated based on a published method. Quartiles of dietary GI (dGI) and glycaemic load (dGL), and intakes of high (CHO_highGI) and low-GI carbohydrates (CHO_lowGI) were derived. Estimated marginal means and standard errors of nutrient and food group intakes by quartiles were calculated using ANCOVA. Odds ratios of not meeting the nutrient reference values for Australia and New Zealand (NRVs) by quartiles of the carbohydrate quality indicators were calculated by logistic regression. Analyses were adjusted for known confounders. **Results:** Participants with higher CHO_highGI had lower intakes of the majority of nutrients examined, except sodium and %energy from free sugars. They were also more than 100% more likely to not meet the NRVs of vitamin A (2.19, 95% CI: 1.89, 2.84), vitamin C (3.93, 95% CI: 1.61, 9.60), vitamin E (2.63, 95% CI: 2.08, 3.31), iron (2.27, 95% CI: 1.48, 3.49), magnesium (2.50, 95% CI: 2.01, 3.12), potassium (2.25, 95% CI: 1.79, 2.83), %EFS (2.74, 95% CI: 2.22, 3.38), and LCN3PUFA (2.35, 95% CI: 1.76, 3.16). Similar results were observed for dGI and dGL, while trends for CHO_highGI were in opposite direction in general. **Conclusions:** Of the carbohydrate quality indicators examined, CHO_highGI was the strongest predictor of nutrient adequacy. Improvement in nutrient adequacy likely contributed to the health protective effect of a low-GI diet.
Low-Calorie Sweeteners

Consumption of Artificial Sweetener Acesulfame Potassium Throughout Pregnancy Induces Glucose Intolerance and Adipose Tissue Dysfunction in Mice


Significance: In a mouse model of pregnancy, high-fructose corn syrup and acesulfame potassium consumption were associated with maternal metabolic dysfunction, reduced fetal growth and fetal hypoglycemia.

Background: Sugar-sweetened beverage consumption is associated with metabolic dysfunction. Artificially sweetened beverages (ASBs) are often promoted as an alternative. However, evidence for the safety of ASB consumption during pregnancy is lacking.

Objectives: The effects of sugar-sweetened beverage and ASB consumption during pregnancy in mice were examined, and we hypothesized that both sugar-sweetened beverages and ASBs would impair maternal metabolic function.

Methods: Pregnant female C57BL/6J mice received control drinking water (CD), high-fructose corn syrup (Fr; 20% kcal intake; 335 mM), or the artificial sweetener acesulfame potassium (AS; 12.5 mM) in their drinking water, from gestational day (GD) 0.5 (n = 8/group). Body weights and food and water intakes were assessed every second day, an oral-glucose-tolerance test (OGTT) was performed at GD 16.5, and mice were culled at GD 18.5. RT-PCR was carried out on adipose tissue, liver, and gut. Adipose tissue morphology was assessed using histological methods. In a separate cohort of animals, pregnancy length was assessed. Repeated-measures ANOVA was performed for the OGTT and weight gain data. All other data were analyzed by 1-way ANOVA. Fr and AS significantly impaired glucose tolerance, as demonstrated by OGTT (21% and 24% increase in AUC, respectively; P = 0.0006).

Results: Fr and AS reduced expression of insulin receptor (39.5% and 33% reduction, respectively; P = 0.02) and peroxisome proliferator-activated receptor γ (45.2% and 47%, respectively; P = 0.039), whereas Fr alone reduced expression of protein kinase B (36.9% reduction; P = 0.048) and resulted in an increase in adipocyte size and leptin concentrations (40% increase; P = 0.03). AS, but not Fr, reduced male fetal weight (16.5% reduction; P = 0.04) and female fetal fasting blood glucose concentration at cull (20% reduction; P = 0.02) compared with CD. AS significantly reduced the length of pregnancy compared with the CD and Fr groups (1.25 d shorter; P = 0.02).

Conclusions: Fr and AS consumption were associated with maternal metabolic dysfunction in mice. AS was also associated with reduced fetal growth and fetal hypoglycemia. Therefore, ASBs may not be a beneficial alternative to sugar-sweetened beverages during pregnancy.

Bioactives

Long-Term Dietary Flavonoid Intake and Risk of Alzheimer Disease and Related Dementias in the Framingham Offspring Cohort


Significance: Analysis of the Framingham Heart Study Offspring Cohort revealed that higher long-term dietary intakes of flavonoids are associated with lower risks of dementia in US adults.

Background: Findings from existing prospective observational studies on the protective associations of flavonoid intake and the risk of Alzheimer disease and related dementias (ADRD) are inconsistent largely due to limitations of these studies. Objectives: To examine the prospective relation between total and 6 classes of dietary flavonoid intake and risk of ADRD and Alzheimer disease (AD) while addressing limitations of earlier observational studies.

Methods: We used data from the Framingham Heart Study Offspring Cohort exams 5 through 9. Participants were ADRD-free with a valid FFQ at baseline. Flavonoid intakes were updated at each exam to represent the cumulative average intake across the 5 exams, and were expressed as percentile categories of intake (≤15th, >15th to 30th, >30th to 60th, >60th) to handle their nonlinear relation with ADRD and AD. Cox proportional hazards regression was used to estimate the HRs for the association between the flavonoid intakes and incidence of ADRD and AD.

Results: Over an average follow-up of 19.7 y in 2801 participants (mean baseline age = 59.1 y; 52% females), there were 193 ADRD events of which 158 were AD. After multivariate and dietary adjustments, individuals with the highest (>60th percentile) intakes of flavonols, anthocyanins, and flavonoid polymers had a lower risk of ADRD relative to individuals with the lowest intakes (≤15th percentile), with HRs (95% CI; P-trend) of 0.54 (0.32, 0.90; P = 0.003) for flavonols, 0.24 (0.15, 0.39; P < 0.001) for anthocyanins, and 0.58 (0.35, 0.94; P = 0.03) for flavonoid polymers. The same pattern of associations was seen with AD for flavonols and anthocyanins but not for flavonoid polymers. Conclusion: Our findings imply that higher long-term dietary intakes of flavonoids are associated with lower risks of ADRD and AD in US adults.
Sodium

The Macronutrient Content of Sodium-Modified Foods Is Unchanged Compared With Regular Counterparts: An Evaluation of Select Categories of Packaged Foods in the United States, 2018


**Significance:** The similarity of the labels for sodium-modified foods and their regular counterparts suggests that reformulation did not include the addition of significant amounts of sugars, fats or other macronutrients.

**Background:** Lowering excess sodium in packaged foods is part of a public health strategy to reduce cardiovascular disease risk. Sales of foods with labeled sodium claims increased during the past decade. Yet, it is unclear whether sugars or fats were added during the reformulation of foods that might counter the benefits of sodium reduction. **Objective:** It was hypothesized that the nutrient content of packaged foods with lower sodium label claims (i.e., sodium-modified) would differ from their regular (i.e., unmodified) counterparts. **Design:** This cross-sectional study compared label data of 153 sodium-modified foods and 141 regular, matched counterparts within four food categories: soups, processed meats, vegetables, and savory snacks. Foods were identified by searching manufacturer websites of the top-10 brands in each category. Sodium, calories, total carbohydrate, sugar, protein, total fat, saturated fat, and potassium (when reported) were compared by labeled serving and per 100 g food.

**Results:** The average amount in milligrams of sodium per serving in regular foods ranged from 162 mg for savory snacks to 782 mg for soups. Compared with regular foods, the matched lower sodium foods had significantly less sodium per serving (-95 to -387 mg) and per 100 g (-184 to -462 mg) (*P*<0.01 for all comparisons), except for soups per 100 g (*P* = 0.166), and were similar to their regular counterparts in calories, total carbohydrate, sugar, protein, total fat, and saturated fat (*P*>0.05 for all comparisons). Of the soups that reported potassium on the label, potassium was 244 mg/serving (*P*=0.004) and 139 mg/100 g (*P*=0.002) higher among matched lower sodium soups.

**Conclusions:** The similarity in macronutrient contents on the labels for sodium-modified foods and their regular counterparts suggests that reformulation did not include the addition of significant amounts of sugars, fats, or other macronutrients among major food brands in the selected categories. Potassium content and additional food categories deserve further investigation.

Gut Microbiome

Profiling of Endogenous and Gut Microbial Metabolites to Indicate Metabotype-Specific Dietary Responses: A Systematic Review


**Significance:** The ability to profile multiple metabolites and the corresponding metabotypes in a single analysis helps decode the complex interplay between diet, other relevant factors and health.

Upon dietary exposure, the endogenous metabolism responds to the diet-derived nutrients and bioactive compounds, such as phytochemicals. However, the responses vary remarkably due to the interplay with other dietary components, lifestyle exposures, and intrinsic factors, which lead to differences in endogenous regulatory metabolism. These physiological processes are evidenced as a signature profile composed of various metabolites constituting metabolic phenotypes, or metabotypes. The metabolic profiling of biological samples following dietary intake hence would provide information about diet-that is, as the intake biomarkers and the ongoing physiological reactions triggered by this intake-thereby enable evaluation of the metabolic basis required to distinguish the different metabotypes. The capacity of nontargeted metabolomics to also encompass the unprecedented metabolite species has enabled the profiling of multiple metabolites and the corresponding metabotypes with a single analysis, decoding the complex interplay between diet, other relevant factors, and health. In this systematic review, we screened 345 articles published in English in January 2007-July 2018, which applied the metabolomics approach to profile the changes of endogenous metabolites in the blood related to dietary interventions, either derived by metabolism of gut microbiota or the human host. We excluded all the compounds that were directly derived from diet, and also the dietary interventions focusing on supplementation with individual compounds. After the removal of less relevant studies and assessment of eligibility, 49 articles were included in this review. First, we mention the contribution of individual factors, either modifiable or nonmodifiable factors, in shaping metabolic profile. Then, how different aspects of the diet would affect the metabolic profiles are disentangled. Next, the classes of endogenous metabolites altered following included dietary interventions are listed. We also discuss the current challenges in the field, along with future research opportunities.