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Nutrition Briefs

North America March 2019

Nutritional Epidemiology

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

Prentice RL, Pettinger M, Neuhouser ML, Tinker LF, Huang Y, Zheng C, et al. *Am J Clin Nutr.* 2019 Mar 27. pii: nqy360. doi: 10.1093/ajcn/nqy360. [Article Link](#)

Significance: Serum-based biomarkers of nutrient and food intake can be applied in disease-association analyses in large epidemiologic cohorts.



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 moderately 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.

Dietary Patterns

The Associations of Fruit and Vegetable Intakes With Burden of Diseases: A Systematic Review of Meta-Analyses

Yip CSC, Chan W, Fielding R. *J Acad Nutr Diet.* 2019 Mar;119(3):464-481. doi: 10.1016/j.jand.2018.11.007. [Article Link](#)

Significance: The findings from this systematic review support current fruit and vegetable intake recommendations.

Background: Low fruit and vegetable intakes are recognized risk factors for noncommunicable diseases. This systematic review summarizes published meta-analyses of global burden of diseases attributable to low fruit and vegetable intakes, and the best relative risk estimates. **Methods:** A published novel assessment process combining Cochrane Review measures, Assessing the Methodological Quality of Systematic Reviews checklist, and Newcastle-Ottawa Quality Assessment Scale was employed. **Results:** Sixty-four reports investigating 98 risk-disease pairs were included in the systematic review. Fifty-six pairs from 39 reports were assessed as statistically significant, involving 29 burden of diseases. Dose responses were identified for 31 negative and two positive associations. High against low intake relative risks were identified for 22 negative and one positive association. The highest identified linear dose response for each 100 g/day increase in fruit intakes was 0.56 (95% CI 0.42 to 0.74) for esophageal

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cancer, followed by 0.72 (95% CI 0.59 to 0.87) for mouth, pharynx, and larynx cancer; nonlinear dose response for the first 100 g/day of fruit intakes were 0.86 (95% CI 0.84 to 0.88) for stroke, followed by 0.89 (95% CI 0.88 to 0.90) for all-cause mortality. The highest identified linear dose response for each 100 g/day increase in vegetable intakes was 0.88 (95% CI 0.80 to 0.95) for renal cell cancer, followed by 0.89 (95% CI 0.84 to 0.95) for non-Hodgkin lymphoma; nonlinear dose responses for the first 100 g/day of vegetable intake were 0.86 (95% CI 0.84 to 0.89) for coronary heart disease, followed by 0.87 (95% CI 0.84 to 0.90) for all-cause mortality. For nonlinear associations, clear increases in protective associations were observed with the first 200 g/day of intakes, whereas little further increase or even decrease in protective associations were reported beyond 300 g/day intakes. Canned fruit intakes were positively associated with all-cause and cardiovascular disease mortality, and pickled vegetable intakes were positively associated with stomach cancer. **Conclusions:** This systematic review supports existing recommendations for fruit and vegetable intakes. Current comparative risk assessments might significantly underestimate the protective associations of fruit and vegetable intakes.

Change in Plant-Based Diet Quality Is Associated With Changes in Plasma Adiposity-Associated Biomarker Concentrations in Women

Baden MY, Satija A, Hu FB, Huang T. *J Nutr.* 2019 Mar 30. pii: nxy301. doi: 10.1093/jn/nxy301. [Article Link](#)

Significance: Adherence to a healthful plant-based diet, but not an unhealthful plant-based diet, is associated with favorable adiposity-associated biomarkers in women.



Background: A healthful plant-based diet is associated with lower risk of cardiometabolic diseases. However, it is still unclear whether such benefits are due to its favorable effects on adiposity-associated biomarkers. **Objective:** We investigated the associations between biomarkers and 3 plant-based diet indices: an overall plant-based diet index (PDI); a healthful plant-based diet index (hPDI); and an unhealthful plant-based diet index (uPDI). **Methods:** In the Nurses' Health Study II, 831 women [baseline mean age: 45 y; body mass index (BMI, kg/m²): 24.6] were randomly selected from those who provided 2 blood samples in 1996–1999 and 2010–2011 to measure plasma concentrations of adiponectin, leptin, soluble leptin receptor (sOB-R), insulin, retinol-binding protein-4, high-sensitivity C-reactive protein (hsCRP), and interleukin-6 (IL-6). Plant-based diet indices were derived from semiquantitative food frequency questionnaires assessed at each blood collection. Linear mixed models were used to evaluate cross-sectional associations, and general linear models were used to evaluate longitudinal associations. **Results:** In cross-sectional analyses with multivariable adjustment including BMI, higher hPDI was associated with lower concentrations of leptin, insulin, and hsCRP, and higher adiponectin and sOB-R concentrations (biomarker differences per 10-point higher hPDI: -7.2%, -10.0%, -13.6%, 3.0%, and 1.9%, respectively; $P \leq 0.025$). A higher uPDI was associated with higher concentrations of leptin and insulin (4.4% and 4.8%, respectively; $P \leq 0.048$). In longitudinal analyses with multivariable adjustment

including weight change, an increase in hPDI (improved plant-based diet quality) was inversely associated with changes in leptin and hsCRP (biomarker changes per 10-point hPDI increase: -7.7% and -17.8%, respectively; $P \leq 0.005$), whereas an increase in uPDI (worsened plant-based diet quality) was positively associated with changes in leptin, hsCRP, and IL-6 (10.1%, 13.5%, and 12.4%, respectively; $P \leq 0.021$). **Conclusions:** Adherence to a healthful plant-based diet is associated with favorable long-term changes in adiposity-associated biomarker concentrations in women.

Protein

Dietary Protein Intake Is Not Associated With 5-Y Change in Mid-Thigh Muscle Cross-Sectional Area by Computed Tomography in Older Adults: The Health, Aging, and Body Composition (Health ABC) Study

Verreijen AM, Engberink MF, Houston DK, Brouwer IA, Cawthon PM, Newman AB, et al. *Am J Clin Nutr.* 2019 Mar 1; 109(3):535-543. doi: 10.1093/ajcn/nqy341. [Article Link](#)

Significance: This study did not find an association between energy-adjusted total, animal, or plant protein intake and mid-thigh muscle cross-sectional area in older adults.

Background: A higher protein intake is suggested to preserve muscle mass during aging and may therefore reduce the risk of sarcopenia. **Objectives:** We explored whether the amount and type (animal or vegetable) of protein intake were associated with 5-y change in mid-thigh muscle cross-sectional area (CSA) in older adults ($n = 1561$). **Methods:** Protein intake was assessed at year 2 by a Block food-frequency questionnaire in participants (aged 70–79 y) of the Health, Aging, and Body Composition (Health ABC) Study, a prospective cohort study. At year 1 and year 6 mid-thigh muscle CSA in square centimeters was measured

by computed tomography. Multiple linear regression analysis was used to examine the association between energy-adjusted protein residuals in grams per day (total, animal, and vegetable protein) and muscle CSA at year 6, adjusted for muscle CSA at year 1 and potential confounders including prevalent health conditions, physical activity, and 5-y change in fat mass. **Results:** Mean (95% CI) protein intake was 0.90 (0.88, 0.92) g · kg⁻¹ · d⁻¹ and mean (95% CI) 5-y change in muscle CSA was -9.8 (-10.6, -8.9) cm². No association was observed between energy-adjusted total ($\beta = -0.00$; 95% CI: -0.06, 0.06 cm²; P = 0.982), animal ($\beta = -0.00$; 95% CI: -0.06, 0.05 cm²; P = 0.923), or plant ($\beta = +0.07$; 95% CI: -0.06, 0.21 cm²; P = 0.276) protein intake and muscle CSA at year 6, adjusted for baseline mid-thigh muscle CSA and potential confounders. **Conclusions:** This study suggests that a higher total, animal, or vegetable protein intake is not associated with 5-y change in mid-thigh muscle CSA in older adults. This conclusion contradicts some, but not all, previous research. This trial was registered at www.trialregister.nl as NTR6930.

Associations of Protein Intake in Early Childhood With Body Composition, Height, and Insulin-Like Growth Factor I in Mid-Childhood and Early Adolescence

Switkowski KM, Jacques PF, Must A, Fleisch A, Oken E. *Am J Clin Nutr.* 2019 Mar 14. pii: nqy354. doi: 10.1093/ajcn/nqy354. [Article Link](#)

Significance: Early childhood protein intake may contribute to programming lean mass and IGF-1 in early adolescence in boys, but no such associations were found in girls.

Background: Early protein intake may program later body composition and height growth, perhaps mediated by insulin-like growth factor I (IGF-I). In infancy, higher protein intake is consistently associated with higher IGF-I concentrations and more rapid growth, but associations of protein intake after infancy with later growth and IGF-I are less clear. **Objectives:** Our objective was to examine associations of protein intake in early childhood (median 3.2 y) with height, IGF-I, and measures of adiposity and lean mass in mid-childhood (median 7.7 y) and early adolescence (median 13.0 y), and with changes in these outcomes over time. We hypothesized that early childhood protein intake programs later growth. **Methods:** We studied 1165 children in the Boston-area Project Viva cohort. Mothers reported children's diet using food-frequency questionnaires. We stratified by child sex and examined associations of early childhood protein intake with mid-childhood and early adolescent BMI z score, skinfold thicknesses, dual-energy X-ray absorptiometry (DXA) fat mass, DXA lean mass, height z score, and IGF-I concentration. We adjusted linear regression models for race/ethnicity, family sociodemographics, parental and birth anthropometrics, breastfeeding status, physical activity, and fast food intake. **Results:** Mean protein intake in early childhood was 58.3 g/d. There were no associations of protein intake in early childhood with any of the mid-childhood outcomes. Among boys, however, each 10-g increase in early childhood total protein intake was associated with several markers of early adolescent size, namely BMI z score (0.12 higher; 95% CI: 0.01, 0.23), DXA lean mass index (1.34% higher; 95% CI: -0.07%, 2.78%), and circulating IGF-I (5.67% higher; 95% CI: 0.30%, 11.3%). There were no associations with fat mass and no associations with any adolescent outcomes among girls. **Conclusions:** Early childhood protein intake may contribute to programming lean mass and IGF-I around the time of puberty in boys, but not to adiposity development. This study was registered at clinicaltrials.gov as NCT02820402.

Carbohydrates

Dietary Fat, Fibre, Satiation, and Satiety—A Systematic Review of Acute Studies

Warrillow A, Mellor D, McKune A, Pumpa K. *Eur J Clin Nutr.* 2019 Mar;73(3):333-344. doi: 10.1038/s41430-018-0295-7. [Article Link](#)

Significance: In a systematic review of acute studies, no effects of fat and fiber on satiety were found.

Background/Objectives: Humans appear to have innate energy regulation mechanisms that manifest in sensations of satiation during a meal and satiety post ingestion. Interactions between these mechanisms and the macronutrient profile of their contemporary food environment could be responsible for the dysregulation of this mechanism, resulting in a higher energy intake. The aim of this systematic review was to determine the impact of dietary fibre and fat both in isolation and combination on satiation and satiety. **Subjects/Methods:** A systematic review of the literature was undertaken, from inception until end December 2017, in accordance with the PRISMA guidelines, in: Scopus, Food Science and Tech, CINAHL, and Medline databases. The search strategy was limited to articles in English language, published in peer-reviewed journals and human studies. Studies were selected based on inclusion/exclusion criteria. **Results:** A total of 1490 studies were found initially using the selected search terms that were reduced to 12 studies suitable for inclusion. Following on from this, a meta-analysis was also conducted to determine any satiety effects from any potential interaction between dietary fat and fibre on satiety, no significant effects were found. **Conclusions:** Owing to high energy density, fat (per kJ) had a weak effect on satiation as determined by the effect per gram for each unit of energy. The addition of fibre theoretically improves satiety by slowing the absorption of various nutrients including fat, although the meta-analysis as part of this review was unable to demonstrate an effect, perhaps reflecting a lack of sensitivity in research design. The potential to improve satiation and satiety responses by consuming fat together with carbohydrates containing fibre warrants further investigation.

Bioactives

Proanthocyanidins of Natural Origin: Molecular Mechanisms and Implications for Lipid Disorder and Aging-Associated Diseases

Nie Y, Stürzenbaum SR. *Adv Nutr*. 2019 Mar 30. pii: nmy118. doi: 10.1093/advances/nmy118. [Article Link](#)

Significance: The current knowledge related to proanthocyanidins in global lipid metabolism and aging are reviewed.

Proanthocyanidins are phytonutrients formed by oligomerization or polymerization of subunits catechin, epicatechin, and their gallic acid esters. Proanthocyanidins are a component of many plants and thus form an integral part of the human diet. Oligomeric proanthocyanidins are currently marketed as medicinal products that target vascular disorders and chronic pathological conditions, many of which are age-associated. Proanthocyanidins are also characterized by their effects on energy homeostasis. Not dissimilar to their chemically synthesized counterparts, naturally extracted proanthocyanidins act via inhibition of lipases, stimulation of energy expenditure, or suppression of appetite. Here we review the current knowledge-base and highlight challenges and future impacts regarding involvement of proanthocyanidins in global lipid metabolism, with a focus on the molecular mechanisms and pathological conditions that progress with aging.

Sodium

2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease

Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. *Circulation*. 2019 Mar 17: CIR0000000000000678. doi: 10.1161/CIR.0000000000000678. [Article Link](#)

This is a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation, the American Geriatrics Society, the American Society of Preventive Cardiology, and the Preventive Cardiovascular Nurses Association.

Lipids

Diets Enriched With Conventional or High-Oleic Acid Canola Oils Lower Atherogenic Lipids and Lipoproteins Compared to a Diet with a Western Fatty Acid Profile in Adults with Central Adiposity

Bowen KJ, Kris-Etherton PM, West SG, Fleming JA, Connelly PW, Lamarche B, et al. *J Nutr*. 2019 Mar 1;149(3):471-478. doi: 10.1093/jn/nxy307. [Article Link](#)

Significance: High-oleic acid canola oil elicited favorable effects on blood lipids and lipoproteins compared to conventional canola oil.



Background: Novel oils high in monounsaturated fatty acids (MUFAs) and low in saturated fatty acids (SFAs) are an alternative to partially hydrogenated oils high in trans-unsaturated fatty acids. There is widespread use of high-MUFA oils across the food industry; however, limited knowledge of their cardiovascular impact exists. **Objectives:** We investigated the effects of diets containing canola oil, high-oleic acid canola oil (HOCO), and a control oil blend (diet formulated to emulate a Western fat profile) on lipids, lipoproteins, and apolipoproteins (apos), as secondary outcomes of the trial. **Methods:** In a multi-center, double-blind, randomized, 3-period crossover, controlled feeding trial, men ($n = 44$) and women ($n = 75$) with a mean age of 44 y, mean body mass index (BMI; in kg/m^2) of 31.7, and an increased waist circumference plus ≥ 1 metabolic syndrome criteria consumed prepared, weight-maintenance diets containing canola oil [17.5% MUFAs, 9.2% polyunsaturated fatty acids (PUFAs), 6.6% SFAs], HOCO (19.1% MUFAs, 7.0% PUFAs, 6.4% SFAs), or control oil (10.5% MUFAs, 10.0% PUFAs, 12.3% SFAs) for 6 wk with ≥ 4 -wk washouts. Fasting serum lipids were assessed at baseline and 6 wk. Diet effects were examined using a repeated measures mixed model. **Results:** Compared with the control, canola and HOCO diets resulted in lower endpoint total cholesterol (TC; -4.2% and -3.4% ; $P < 0.0001$), LDL cholesterol (-6.6% and -5.6% ; $P < 0.0001$), apoB (-3.7% and -3.4% ; $P = 0.002$), and non-HDL cholesterol (-4.5% and -4.0% ; $P = 0.001$), with no differences between canola diets. The TC:HDL cholesterol and apoB:apoA1 ratios were lower after the HOCO diet than after the control diet (-3.7% and -3.4% , respectively). There were no diet effects on triglyceride, HDL cholesterol, or apoA1 concentrations. **Conclusions:** HOCO, with increased MUFAs at the expense of decreased PUFAs, elicited beneficial effects on lipids and lipoproteins comparable to conventional canola oil and consistent with reduced cardiovascular disease risk in adults with central adiposity. This trial was registered at www.clinicaltrials.gov as NCT02029833.

Microbiome

Modulation of the Gut Microbiota by Resistant Starch as a Treatment of Chronic Kidney Diseases: Evidence of Efficacy and Mechanistic Insights

Snelson M, Kellow NJ, Coughlan MT. *Adv Nutr*. 2019 Mar 1;10(2):303-320. doi: 10.1093/advances/nmy068. [Article Link](#)

Significance: Resistant starch may alter gut microbial communities and confer changes in gut metabolites that lead to attenuated progression of chronic kidney disease.

Chronic kidney disease (CKD) has been associated with changes in gut microbial ecology, or “dysbiosis,” which may contribute to disease progression. Recent studies have focused on dietary approaches to favorably alter the composition of the gut microbial communities as a treatment method in CKD. Resistant starch (RS), a prebiotic that promotes proliferation of gut bacteria such as *Bifidobacteria* and *Lactobacilli*, increases the production of metabolites including short-chain fatty acids, which confer a number of health-promoting benefits. However, there is a lack of mechanistic insight into how these metabolites can positively influence renal health. Emerging evidence shows that microbiota-derived metabolites can regulate the incretin axis and mitigate inflammation via expansion of regulatory T cells. Studies from animal models and patients with CKD show that RS supplementation attenuates the concentrations of uremic retention solutes, including indoxyl sulfate and p-cresyl sulfate. Here, we present the current state of knowledge linking the microbiome to CKD, we explore the efficacy of RS in animal models of CKD and in humans with the condition, and we discuss how RS supplementation could be a promising dietary approach for slowing CKD progression.

Effects of Oral Supplementation With Probiotics or Synbiotics in Overweight and Obese Adults: A Systematic Review and Meta-Analyses of Randomized Trials

Suzumura EA, Bersch-Ferreira AC, Torreglosa CR, da Silva JT, Coqueiro AY, Kuntz MGF, et al. *Nutr Rev*. 2019 Mar 28. pii: nuz001. doi: 10.1093/nutrit/nuz001. [Article Link](#)

Significance: This systematic review and meta-analysis found low- to moderate-quality evidence that oral supplementation with probiotics or synbiotics may lead to a small reduction in waist circumference, with no effect on body weight or BMI.

Context: Recent evidence suggests that modulation of the gut microbiota may contribute to body weight control. **Objective:** This systematic review aimed to assess the effects of oral supplementation with probiotics or synbiotics on body weight, body mass index (BMI), and waist circumference in overweight and obese adults (BMI \geq 25 kg/m²). **Data Sources:** Five electronic databases—PubMed, Embase, Cochrane Library/CENTRAL, LILACS, and Web of Science—were searched from inception to August 2017. No language restrictions were applied. **Study Selection:** Randomized and quasi-randomized parallel trials that assessed the effects of oral supplementation with probiotics or synbiotics vs any other intervention but bariatric surgery or fecal transplantation in overweight or obese adults were selected. **Data Extraction:** Three teams of 2 authors independently assessed risk of bias and extracted data from the included trials. Data were pooled using inverse-variance random-effects meta-analyses. The quality of evidence was assessed using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system. **Results:** Nineteen randomized trials (28 publications, 1412 participants) were included. There were no differences in mean body weight change [mean difference (MD), -0.54 kg; 95%CI, -1.09 to 0.01; I²=0%; moderate quality of evidence) or mean BMI change (MD, -0.19 kg/m²; 95%CI, -0.43 to 0.04; I²=51%; low quality of evidence) between groups who received probiotics or synbiotics and control groups. Oral supplementation with probiotics or synbiotics reduced mean waist circumference compared with control (MD, -0.82 cm; 95%CI, -1.43 to -0.21; I²=46%; low quality of evidence). **Conclusions:** The findings suggest that oral supplementation with probiotics or synbiotics has a small effect to reduce waist circumference but no effect on body weight or BMI, although the quality of evidence is low to moderate. Therefore, the current evidence is not definitive. Large-scale trials are needed and may help to better inform clinical practice. **Systematic Review Registration:** PROSPERO registration number CRD42018075126.
