Nutrition Research Methodology

**Perspective: Proposed Harmonized Nutrient Reference Values for Populations**


**Significance:** This review demonstrates an approach for harmonizing the nutrient intake reference values for average requirements and tolerable upper level of intakes that can be applied on a global scale for assessing intakes across populations.

Two core nutrient intake reference values (NRVs) are required for assessing the adequacy and safety of nutrient intakes for population groups: the average requirement (AR) and the tolerable upper level of intake (UL). Applications of such assessments include providing advice to improve intakes, formulating complementary foods, estimating the amounts of nutrients to be added to fortified foods and monitoring changes in intake, and product labeling at the global, national, or regional level. However, there is a lack of unity across country-level organizations in the methodological approach used to derive NRVs, and ARs and ULs are lacking in many compilations, thus limiting the ability to assess nutrient intakes for their population groups. Because physiological requirements vary little across populations globally, and setting reference values requires determining an acceptable level of uncertainty, it is feasible to adapt current recommendations from different sources to harmonize these core reference values. The objective of this review is to demonstrate an approach for harmonizing the NRVs for ARs (here termed “H-ARs”) and ULs (“H-ULs”) that can be applied on a global scale to assessing intakes across populations. The approach incorporates the framework and terminology recommended by reports from the United Nations University, the National Academies of Sciences, Engineering, and Medicine (NASEM), the Institute of Medicine (IOM), and the European Food Safety Authority (EFSA). After reviewing available alternatives, the proposed harmonized values were selected from standards set by EFSA (for Europe) and the IOM (for the United States and Canada), giving priority to those published most recently. Justifications for the proposed values are presented, along with discussion of their limitations. Ideally, these methods should be further reviewed by an international group of experts. Meanwhile, the H-ARs and H-ULs suggested in this review can be used to assess intakes of populations for many applications in global and regional contexts.

**Dietary Patterns**

**Impact of Nutrition on Telomere Health: Systematic Review of Observational Cohort Studies and Randomized Clinical Trials**


**Significance:** The results from this systematic review suggest that some antioxidant nutrients, the consumption of fruits and vegetables, and Mediterranean diet are associated with longer telomeres.

Diet, physical activity, and other lifestyle factors have been implicated in the pathophysiology of several chronic diseases, but also in a lower total mortality and longer life expectancy. One of the mechanisms in which diet can reduce the risk of disease is with regard to its impact on telomeres. Telomere length (TL) is highly correlated to chronological age and metabolic status. Individuals with shorter telomeres are at higher risk of chronic diseases and mortality. Diet may influence TL by several mechanisms such as regulating oxidative stress and inflammation or modulating epigenetic reactions. The present systematic review aims to examine the results from epidemiologic and clinical trials conducted in humans evaluating the role of nutrients, food groups, and dietary patterns on TL. We also discuss the possible mechanisms of action that influence this process, with the perspective that TL could be a novel biomarker indicating the risk of metabolic disturbances and age-related diseases. The available evidence suggests that some antioxidant nutrients, the consumption of fruits and vegetables, and Mediterranean
diet are mainly associated with longer telomeres. However, most of the evidence is based on high heterogenic observational studies and very few randomized clinical trials (RCTs). Therefore, the associations summarized in the present review need to be confirmed with larger prospective cohort studies and better-designed RCTs.

Protein

High Compared With Moderate Protein Intake Reduces Adaptive Thermogenesis and Induces a Negative Energy Balance during Long-term Weight-Loss Maintenance in Participants with Prediabetes in the Postobese State: A PREVIEW Study


Significance: Relative to a moderate-protein diet, consumption of a high-protein diet led to a negative energy balance and counteracted adaptive thermogenesis after weight loss in participants with prediabetes in the postobese state.

Background: Weight loss has been associated with adaptations in energy expenditure. Identifying factors that counteract these adaptations are important for long-term weight loss and weight maintenance. Objective: The aim of this study was to investigate whether increased protein/carbohydrate ratio would reduce adaptive thermogenesis (AT) and the expected positive energy balance (EB) during weight maintenance after weight loss in participants with prediabetes in the postobese state. Methods: In 38 participants, the effects of 2 diets differing in protein/carbohydrate ratio on energy expenditure and respiratory quotient (RQ) were assessed during 48-h respiration chamber measurements ∼34 mo after weight loss. Participants consumed a high-protein (HP) diet (n = 20; 13 women/7 men; age: 64.0 ± 6.2 y; BMI: 28.9 ± 4.0 kg/m 2) with 25:45:30% or a moderate-protein (MP) diet (n = 18; 9 women/9 men; age: 65.1 ± 5.8 y; BMI: 29.0 ± 3.8 kg/m 2) with 15:55:30% of energy from protein:carbohydrate:fat. Predicted resting energy expenditure (REEp) was calculated based on fat-free mass and fat mass. AT was assessed by subtracting measured resting energy expenditure (REE) from REEp. The main outcomes included differences in components of energy expenditure, substrate oxidation, and AT between groups. Results: EB (MP: 0.2 ± 0.9 MJ/d; HP: −0.5 ± 0.9 MJ/d) and RQ (MP = 0.84 ± 0.02; HP = 0.82 ± 0.02) were reduced and REE (MP: 7.3 ± 0.2 MJ/d compared with HP: 7.8 ± 0.2 MJ/d) was increased in the HP group compared with the MP group (P < 0.05). REE was different from REEp in the HP group, whereas REE was lower than REEp in the MP group (P < 0.05). Furthermore, EB was positively related to AT (rs = 0.74; P < 0.001) and RQ (rs = 0.47; P < 0.01) in the whole group of participants. Conclusions: In conclusion, an HP diet compared with an MP diet led to a negative EB and counteracted AT ∼34 mo after weight loss, in participants with prediabetes in the postobese state. These results indicate the relevance of compliance to an increased protein/carbohydrate ratio for long-term weight maintenance after weight loss. The trial was registered at clinicaltrials.gov as NCT01777893.

Lipids

Impact of Isocaloric Exchanges of Carbohydrate for Fat on Postprandial Glucose, Insulin, Triglycerides, and Free Fatty Acid Responses—A Systematic Review and Meta-Analysis


Significance: This systematic review and meta-analysis of RTCs quantifies the effect size of exchanging carbohydrates for fat in mixed meals on postprandial glucose, insulin, triglycerides, and free fatty acid responses.

Varying the macronutrient composition of meals alters acute postprandial responses, but the effect sizes for specific macronutrient exchanges have not been quantified by systematic reviews. Therefore the aim is to quantify the effect size of exchanging fat for carbohydrates in mixed meals on postprandial glucose (PPG), insulin (PI), triglycerides (PPTG), and free fatty acids (PPFFA) responses by performing a systematic review and meta-analysis of randomized controlled trials. A systematic literature search was undertaken on randomized controlled trials comparing isocaloric high fat with high carbohydrate meals, with comparable protein contents and at least one postprandial glycemic- and one lipid outcome. The outcome data were extracted and expressed as mean postprandial levels over 2 h. Ten studies involving 14 comparisons met the eligibility criteria. Data were available for meta-analysis from 347 participants, consuming mixed meals containing 250-1003 kcal, and total fat contents of 33.3-75.6 percentage of energy (en%) (intervention) versus 0-31.7 en% (control). Each 10e% increase in fat, replacing carbohydrates produced a mean reduction in PPG of 0.32 mmol/l (95% CI -0.64 to -0.00, p = 0.047), a reduction in PPI of 18.2 pmol/l (95% CI -24.86 to -11.54), an increase in PPTG of 0.06 mmol/l (95% CI 0.02 to 0.09, p = 0.004), with no statistically significant effect on PPFFA. Modest exchange of carbohydrates for fats in mixed meals significantly reduces PPG and PPI and increases PPTG responses. The quantitative relationships derived here may be applied to predict responses, and to design and optimize meal macronutrient compositions in dietary intervention studies.
**Dietary Fat and Cardiovascular Disease: Ebb and Flow Over the Last Half Century**

**Significance:** The available evidence to date suggests that dietary guidance consistent with replacing foods high in saturated fat with foods high in unsaturated fat, first recommended more than 50 years ago, remains appropriate to this day.

Dietary modification has been the cornerstone of cardiovascular disease (CVD) prevention since the middle of the last century when the American Heart Association (AHA) first issued recommendations. For the vast majority of that time the focus has been on saturated fat, with or without concomitant guidance for total or unsaturated fat. Over the past few years there has been a renewed debate about the relation between dietary saturated fat and CVD risk, prompted by a series of systematic reviews that have come to what appears to be different conclusions. This triggered a robust discourse about this controversy in the media that in turn has led to confusion in the general public. The genesis of the different conclusions among the systematic reviews has been identified in several studies on the basis of isocaloric substitution analyses. When the data were analyzed on the basis of polyunsaturated fat replacing saturated fat, there was a null relation between dietary saturated fat and CVD. When the substitution macronutrient was not taken into consideration, the differential effects of the macronutrient substitution went unrecognized and the relations judged as null. The lack of distinction among substituted macronutrients accounted for much of what appeared to be discrepancies. Dietary guidance consistent with replacing foods high in saturated fat with foods high in unsaturated fat, first recommended more than 50 y ago, remains appropriate to this day.

**Carbohydrates**

**Dietary Sugars and Cardiometabolic Risk Factors: A Network Meta-Analysis on Isocaloric Substitution Interventions**

**Significance:** In this network meta-analysis, substitution of sucrose and fructose with starch yielded lower LDL cholesterol, while insulin resistance and uric acid concentrations were beneficially affected by replacement of fructose with glucose.

**Background:** There is controversy on the relevance of dietary sugar intake for cardiometabolic health. **Objective:** The aim of this network meta-analysis (NMA) was to assess how isocaloric substitutions of dietary sugar with other carbohydrates affect cardiometabolic risk factors, comparing different intervention studies. **Methods:** We included randomized controlled trials (RCTs) investigating the isocaloric effect of substituting dietary sugars (fructose, glucose, sucrose) with other sugars or starch on cardiometabolic risk markers, including LDL cholesterol, triacylglycerol (TG), fasting glucose (FG), glycated hemoglobin (HbA1c), insulin resistance (HOMA-IR), uric acid, C-reactive protein (CRP), alanine transaminase (ALT), and liver fat content. To identify the most beneficial intervention for each outcome, random-effects NMA was conducted by calculating pooled mean differences (MDs) with 95% CIs, and by ranking the surface under the cumulative ranking curves (SUCRAs). The certainty of evidence was evaluated using the Confidence In Network Meta-Analysis tool. **Results:** Thirty-eight RCTs, including 1383 participants, were identified. A reduction in LDL-cholesterol concentrations was shown for the exchange of sucrose with starch (MD: −0.23 mmol/L; 95% CI: −0.38, −0.07 mmol/L) or fructose with starch (MD: −0.22 mmol/L; 95% CI: −0.39, −0.05 mmol/L; SUCRAs: 98%). FG concentrations were also lower for the exchange of sucrose with starch (MD: −0.14 mmol/L; 95% CI: −0.29, 0.01 mmol/L; SUCRAs: 91%). Replacing fructose with an equivalent energy amount of glucose reduced HOMA-IR (MD: −0.36; 95% CI: −0.71, −0.02; SUCRAs: 74%) and uric acid (MD: −23.77 µmol/L; 95% CI: −44.21, −3.32 µmol/L; SUCRAs: 93%). The certainty of evidence was rated very low to moderate. No significant effects were observed for TG, HbA1c, CRP, ALT, and AST. **Conclusions:** Our findings indicate that substitution of sucrose and fructose with starch yielded lower LDL cholesterol. Insulin resistance and uric acid concentrations were beneficially affected by replacement of fructose with glucose. Our findings are limited by the very low to moderate certainty of evidence. This review was registered at www.crd.york.ac.uk/prospero as CRD42018080297.
Low-Calorie Sweeteners

Adaptation of the Gut Microbiota to Modern Dietary Sugars and Sweeteners

**Significance:** This review highlights how sugars and sweeteners affect gut microbes through transcriptional, abundance, and genetic adaptations.

The consumption of sugar has become central to the Western diet. Cost and health concerns associated with sucrose spurred the development and consumption of other sugars and sweeteners, with the average American consuming 10 times more sugar than 100 y ago. In this review, we discuss how gut microbes are affected by changes in the consumption of sugars and other sweeteners through transcriptional, abundance, and genetic adaptations. We propose that these adaptations result in microbes taking on different metabolic, ecological, and genetic profiles along the intestinal tract. We suggest novel approaches to assess the consequences of these changes on host-microbe interactions to determine the safety of novel sugars and sweeteners.

Bioactives

Dietary Intakes of Flavan-3-Ols and Cardiometabolic Health: Systematic Review and Meta-Analysis of Randomized Trials and Prospective Cohort Studies

**Significance:** This systematic review and meta-analysis found that the available evidence supports a beneficial effect of flavan-3-ol intake on cardiometabolic outcomes.

This work was supported by the ILSI North America Bioactives Committee.

**Background:** Although available data suggest that some dietary flavan-3-ol sources reduce cardiometabolic risk, to our knowledge no review has systematically synthesized their specific contribution. **Objective:** We aimed to examine, for the first time, if there is consistent evidence that higher flavan-3-ol intake, irrespective of dietary source, reduces cardiometabolic risk. **Methods:** MEDLINE, Cochrane Central, and Commonwealth Agricultural Bureau abstracts were searched for prospective cohorts and randomized controlled trials (RCTs) published from 1946 to March 2019 on flavan-3-ol intake and cardiovascular disease (CVD) risk. Random-effects models meta-analysis was used. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach assessed the strength of evidence. **Results:** Of 15 prospective cohorts (23 publications), 4 found highest compared with lowest habitual intakes of flavan-3-ols were associated with a 13% reduction in risk of CVD mortality and 2 found a 19% reduction in risk of chronic heart disease (CHD) incidence. Highest compared with lowest habitual intakes of monomers were associated with a reduction in risk of type 2 diabetes mellitus (T2DM) (n = 5) and stroke (n = 4) (10% and 18%, respectively). No association was found for hypertension. Of 156 RCTs, flavan-3-ol intervention resulted in significant improvements in acute/chronic flow-mediated dilation (FMD), systolic (SBP) and diastolic blood pressure (DBP), total cholesterol (TC), LDL and HDL cholesterol, triglycerides (TGs), hemoglobin A1c (HbA1c), and homeostasis model assessment of insulin resistance (HOMA-IR). All analyses, except HbA1c, were associated with moderate/high heterogeneity. When analyses were limited to good methodological quality studies, improvements in TC, HDL cholesterol, SBP, DBP, HOMA-IR, and acute/chronic FMD remained significant. In GRADE evaluations, there was moderate evidence in cohort studies that flavan-3-ol and monomer intakes were associated with reduced risk of CVD mortality, CHD, stroke, and T2DM, whereas RCTs reported improved TC, HDL cholesterol, SBP, and HOMA-IR. **Conclusions:** Available evidence supports a beneficial effect of flavan-3-ol intake on cardiometabolic outcomes, but there was considerable heterogeneity in the meta-analysis. Future research should focus on an integrated intake/biomarker approach in cohorts and high-quality dose–response RCTs. This review was registered at www.crd.york.ac.uk/PROSPERO/ as CRD42018035782.

Sodium

Comparison of 24-Hour Urine and 24-Hour Diet Recall for Estimating Dietary Sodium Intake in Populations: A Systematic Review and Meta-Analysis

**Significance:** The findings from this systematic review and meta-analysis suggest that high-quality 24-hour diet recall is an acceptable method of measuring mean population sodium intake if 24-hour urine is not feasible.

This systematic literature review and meta-analysis examined whether 24-hour diet recall is a valid way to measure mean population sodium intake compared with the gold standard 24-hour urinary assessment. The authors searched electronic databases
MEDLINE, Embase, and Scopus using pre-defined terms. Studies were eligible for inclusion if they assessed adult humans in free-living settings, and if they included group means for 24-hour diet recall and 24-hour urinary collection of sodium intake in the same participants. Studies that included populations with an active disease state that might interfere with normal sodium metabolism were excluded. Results of 28 studies are included in the meta-analysis. Overall, 24-hour diet recall underestimated population mean sodium intake by an average of 607 mg per day compared to the 24-hour urine collection. The difference between measures from 24-hour urine and 24-hour diet recall was smaller in studies conducted in high-income countries, in studies where multiple-pass methods of 24-hour diet recall were reported and where urine was validated for completeness. Higher quality studies also reported smaller differences between measures than lower quality studies. Monitoring of population sodium intake with 24-hour urinary excretion remains the most accurate method of assessment. Twenty-four-hour diet recall tends to underestimate intake, although high-quality 24-hour diet recall improves accuracy, and may be used if 24-hour urine is not feasible.

**Gut Microbiome**

The Role of the Gut Microbiome in Predicting Response to Diet and the Development of Precision Nutrition Models-Part I: Overview of Current Methods


Significance: This article is the first in a 2-part review of current research investigating the contribution of the gut microbiota to interindividual variability in response to diet.

Health care is increasingly focused on health at the individual level. In the rapidly evolving field of precision nutrition, researchers aim to identify how genetics, epigenetics, and the microbiome interact to shape an individual’s response to diet. With this understanding, personalized responses can be predicted and dietary advice can be tailored to the individual. With the integration of these complex sources of data, an important aspect of precision nutrition research is the methodology used for studying interindividual variability in response to diet. This article stands as the first in a 2-part review of current research investigating the contribution of the gut microbiota to interindividual variability in response to diet. Part I reviews the methods used by researchers to design and carry out such studies as well as the statistical and bioinformatic methods used to analyze results. Part II reviews the findings of these studies, discusses gaps in our current knowledge, and summarizes directions for future research. Taken together, these reviews summarize the current state of knowledge and provide a foundation for future research on the role of the gut microbiome in precision nutrition.

Read Part II: Results. Article Link

**Personalized Nutrition**

Perspective: Metabotyping—A Potential Personalized Nutrition Strategy for Precision Prevention of Cardiometabolic Disease


Significance: This Perspective reviews the current literature on metabotyping in the context of cardiometabolic disease prevention, and suggests potential strategies for future work to enable metabotype-based nutritional advice.

Diet is an important, modifiable lifestyle factor of cardiometabolic disease risk, and an improved diet can delay or even prevent the onset of disease. Recent evidence suggests that individuals could benefit from diets adapted to their genotype and phenotype: that is, personalized nutrition. A novel strategy is to tailor diets for groups of individuals according to their metabolic phenotypes (metabotypes). Randomized controlled trials evaluating metabotype-specific responses and nonresponses are urgently needed to bridge the current gap of knowledge with regard to the efficacy of personalized strategies in nutrition. In this Perspective, we discuss the concept of metabotyping, review the current literature on metabotyping in the context of cardiometabolic disease prevention, and suggest potential strategies for metabotype-based nutritional advice for future work. We also discuss potential determinants of metabotypes, including gut microbiota, and highlight the use of metabolomics to define effective markers for cardiometabolic disease-related metabotypes. Moreover, we hypothesize that people at high risk for cardiometabolic diseases have distinct metabotypes and that individuals grouped into specific metabotypes may respond differently to the same diet, which is being tested in a project of the Joint Programming Initiative: A Healthy Diet for a Healthy Life.