Reproducibility and Validity of A Posteriori Dietary Patterns: A Systematic Review


**Significance:** This systematic review of reproducibility and validity of a posteriori dietary patterns found that only suggestive conclusions can be derived on reproducibility across different statistical solutions.

The effective use of dietary patterns (DPs) remains limited. There is a need to assess their consistency over multiple administrations of the same dietary source, different dietary sources, or across different studies. Similarly, their generalizability should be based on a previous assessment of DP construct validity. However, to date, no systematic reviews of reproducibility and validity of a posteriori DPs have been carried out. In addition, several methodological questions related to their identification are still open and prevent a fair comparison of epidemiological results on DPs and disease. A systematic review of the literature on the PubMed database was conducted. We identified 218 articles, 64 of which met the inclusion criteria. Of these, the 38 articles dealing with reproducibility and relative and construct validity of DPs were included. These articles (published in 1999–2017, 53% from 2010 onwards) were based on observational studies conducted worldwide. The 14 articles that assessed DP reproducibility across different statistical solutions examined different research questions. Included were: the number of food groups or subjects; input variable format (as well as adjustment for energy intake); algorithms and the number of DPs to retain in cluster analysis; rotation method; and score calculation in factor analysis. However, we identified at most 3 articles per research question on DP reproducibility across statistical solutions. From another 15 articles, reproducibility of DPs over shorter (≤1 y) time periods was generally good and higher than DP relative validity (as measured across different dietary sources). Confirmatory factor analysis was used in 15 of the included articles. It provided reassuring results in identifying valid dietary constructs characterizing the populations under consideration. Based on the available evidence, only suggestive conclusions can be derived on reproducibility across different statistical solutions. Nevertheless, most identified DPs showed good reproducibility, fair relative validity, and good construct validity.

Protein

Plant-Protein Diversity Is Critical to Ensuring the Nutritional Adequacy of Diets When Replacing Animal With Plant Protein: Observed and Modeled Diets of French Adults (INCA3)


**Significance:** This study found that overall diet quality was weakly associated with total and protein diversity and more strongly with plant-protein diversity.

**Background:** There is a current trend in Western countries toward increasing the intake of plant protein. A higher plant-protein intake has been associated with nutritional and health benefits, but these may depend on the pattern of plant-protein sources. **Objective:** We hypothesized that the diversity of plant foods could be important to nutrient adequacy when increasing plant-protein intake in the diet. **Methods:** Using data on 1341 adults (aged 18–64 y) from a representative French national dietary survey conducted in 2014–2015 (the third Individual and National Study on Food Consumption Survey—INCA3), we studied the links between plant-protein intake, dietary diversity (using various dimensions), and nutrient adequacy [assessed using the PANDiet (Probability of Adequate Nutrient Intake) scoring system, comprising adequacy (AS) and moderation (MS) subscores]. We simulated substituting plant-protein foods for animal-protein foods using different models of plant-protein diversity. **Results:** We found that overall diet quality was weakly associated with total and protein diversity and more strongly with plant-protein diversity.
diversity. Plant-protein intake was inversely associated with animal-protein intake, and positively with the PANd diet and MS, but not with the AS. Plant-protein intake displayed little diversity, mostly taking the form of grains (61% of plant-protein intake), and this diversity was even less marked under a higher plant-protein intake. Finally, modeled substitutions showed that reducing animal-protein intake increased the MS (by 32%) in a similar manner whichever plant protein was used for substitution, whereas it decreased the AS (by 20%) unless using a highly diversified plant-protein mix. These simulated improvements in overall adequacy included marked decreases in inadequacy regarding certain nutrients that are typically of animal origin. Conclusions: We conclude that in French adults the current pattern of plant-protein intake is hindering the nutritional benefits of a transition toward more plant protein, indicating that the consumption of plant-protein-based foods other than refined grains should be encouraged.

**Lipids**

**Predicting the Effects of Supplemental EPA and DHA on the Omega-3 Index**


**Significance:** A model was developed to estimate the omega-3 index response to a given EPA + DHA dose and chemical form.

**Background:** Supplemental long-chain omega-3 (n–3) fatty acids (EPA and DHA) raise erythrocyte EPA + DHA [omega-3 index (O3I)] concentrations, but the magnitude or variability of this effect is unclear. **Objective:** The purpose of this study was to model the effects of supplemental EPA + DHA on the O3I. **Methods:** Deidentified data from 1422 individuals from 14 published n–3 intervention trials were included. Variables considered included dose, baseline O3I, sex, age, weight, height, chemical form [ethyl ester (EE) compared with triglyceride (TG)], and duration of treatment. The O3I was measured by the same method in all included studies. Variables were selected by stepwise regression using the Bayesian information criterion. **Results:** Individuals supplemented with EPA + DHA (n = 846) took a mean ± SD of 1983 ± 1297 mg/d, and the placebo controls (n = 576) took none. The mean duration of supplementation was 13.6 ± 6.0 wk. The O3I increased from 4.9% ± 1.7% to 8.1% ± 2.7% in the supplemented individuals (P < 0.0001). The final model included dose, baseline O3I, and chemical formulation type (EE or TG), and these explained 62% of the variance in response (P < 0.0001). The model predicted that the final O3I (and 95% CI) for a population like this, with a baseline concentration of 4.9%, given 850 mg/d of EPA + DHA EE would be ∼6.5% (95% CI: 6.3%, 6.7%). Gram for gram, TG-based supplements increased the O3I by about 1 percentage point more than EE products. **Conclusions:** Of the factors tested, only baseline O3I, dose, and chemical formulation were significant predictors of O3I response to supplementation. The model developed here can be used by researchers to help estimate the O3I response to a given EPA + DHA dose and chemical form.

**Carbohydrates**

**Fiber Intake Predicts Weight Loss and Dietary Adherence in Adults Consuming Calorie-Restricted Diets: The POUNDS Lost (Preventing Overweight Using Novel Dietary Strategies) Study**


**Significance:** This study found evidence to support that dietary fiber intake promotes weight loss and dietary adherence in adults with overweight or obesity consuming a calorie-restricted diet, independently of macronutrient and caloric intake.

**Background:** The effects of dietary composition on weight loss are incompletely understood. In addition to energy intake, fiber intake, energy density, macronutrient composition, and demographic characteristics have all been suggested to contribute to weight loss. **Objective:** The primary aim of this analysis was to assess the role of dietary fiber as a predictor of weight loss in participants who consumed calorie-restricted diets (−750 kcal/d from estimated energy needs) for 6 mo, using data from the POUNDS Lost (Preventing Overweight Using Novel Dietary Strategies) Study—a randomized trial that examined the effects of calorie-restricted diets varying in macronutrient composition on weight loss in adults. **Methods:** Data were randomly partitioned to a training data set (70%) in which the effects of fiber and other weight-loss predictors were identified using adjusted Least Absolute Shrinkage and Selection Operator and model averaging. The retained predictors were then fit on the testing data set to assess predictive performance. **Results:** Three hundred and forty-five participants (53.9% female) provided dietary records at baseline and 6 mo. Mean ± SD age and BMI for the full sample was 52.5 ± 8.7 y and 32.6 ± 3.9 kg/m2, respectively. Mean ± SD (99% CI) weight change at 6 mo for the full sample was −7.27 ± 5.6 kg (−8.05, −6.48 kg). The final, best fit model (R² = 0.41) included fiber, energy density, fat, age, adherence, baseline weight, race, and changes from baseline in carbohydrate, fiber, PUFA, and MUFA intake, but the most influential predictor was fiber intake (β^ = −0.37; P < 0.0001). In addition, fiber was strongly associated with adherence to the macronutrient prescriptions (P < 0.0001). Interactions between race and adherence, age, baseline weight, carbohydrate, energy density, and MUFAs were also retained in the final model. **Conclusion:** Dietary fiber intake, independently of macronutrient and caloric intake, promotes weight loss and dietary adherence in adults with overweight or obesity consuming a calorie-restricted diet. This trial was registered at clinicaltrials.gov as NCT00072995.
Low-Calorie Sweeteners

Lack of Potential Carcinogenicity for Sucralose — Systematic Evaluation and Integration of Mechanistic Data Into the Totality of the Evidence

Significance: The findings from this evaluation of mechanistic data support prior conclusions that sucralose is unlikely to be carcinogenic in humans.

Sucralose is widely used as a sugar substitute. Many studies and authoritative reviews have concluded that sucralose is non-carcinogenic, based primarily on animal cancer bioassays and genotoxicity data. To add to the body of knowledge on the potential carcinogenicity of sucralose, a systematic assessment of mechanistic data was conducted. This entailed using a framework developed for the quantitative integration of data related to the proposed key characteristics of carcinogens (KCCs). Data from peer-reviewed literature and the ToxCast/Tox21 database were evaluated using an algorithm that weights data for quality and relevance. The resulting integration demonstrated an overall lack of activity for sucralose across the KCCs, with no “strong” activity observed for any KCC. Almost all data collected demonstrated inactivity, including those conducted in human models. The overall lack of activity in mechanistic data is consistent with findings from animal cancer bioassays. The few instances of activity across the KCC were generally accompanied by limitations in study design in the context of either quality and/or dose and model relevance, highlighted upon integration of the totality of the evidence. The findings from this comprehensive and integrative evaluation of mechanistic data support prior conclusions that sucralose is unlikely to be carcinogenic in humans.

Lack of Potential Carcinogenicity for Aspartame — Systematic Evaluation and Integration of Mechanistic Data Into the Totality of the Evidence

Significance: This KCC-based analysis, together with the lack of consistent evidence of carcinogenicity in experimental animals, continues to support a lack of carcinogenicity from aspartame consumption.

Despite repeated confirmation of aspartame safety in a variety of foods and beverages, there continues to be interest in researching the potential carcinogenic risk associated with its consumption. The objective of this evaluation was to conduct a systematic assessment of available mechanistic data using a framework for quantitatively integrating the key characteristics of carcinogens (KCCs). For aspartame, 1332 endpoints were appraised for quality and relevance, and quantitatively integrated using an algorithm to determine the potential for individual KCC activity based on all available evidence, and subsequently assessed in the context of human and animal evidence streams. An overall lack of activity (integrated scores <0 and no “strong” categorizations) was observed for all KCCs except oxidative stressor (#5), for which activity was determined to be unlikely to be related to a carcinogenic response. Overall, the KCC-based analysis, together with the lack of consistent evidence of carcinogenicity in experimental animals, continue to support lack of carcinogenicity from aspartame consumption. This comprehensive evaluation of available mechanistic data demonstrates the need for a systematic approach to identify and appraise all available data as part of weight-of-evidence determinations related use of KCC in evaluations of potential human carcinogenicity.

Bioactives

Contribution of Plant Food Bioactives in Promoting Health Effects of Plant Foods: Why Look at Interindividual Variability?

Significance: Capturing the interindividual variability in response to plant food bioactive intake is a crucial step that will enable the development and production of plant food products to satisfy nutritional needs and confer benefits to different categories of the population.

Purpose: Research has identified plant-based diets as the most protective for our health; it is now essential to focus on good food associations and the beneficial constituents in plant foods. From a growing body of evidence, some categories of food phytochemicals are increasingly considered to play a crucial role in the cardiometabolic health effects associated with plant food consumption. However, the heterogeneity in responsiveness to plant food bioactive intake that is frequently observed in clinical trials can hinder the identification of the effects of these compounds in specific subpopulations and likely lead to underestimating their actual contribution to the health effects of their food sources. Results: The magnitude and the main factors responsible for this between-subject variation in response to the consumption of the major families of food phytochemicals have been poorly documented so far. Thus, research efforts in this area must be developed. More importantly, capturing the
interindividual variability in response to plant food bioactive intake, together with identifying the main determinants involved, is a crucial step that will enable the development and production of plant food products, thereby satisfying the nutritional needs and conferring benefits to different categories of populations. Conclusion: The development of a science-based personalized nutrition approach focusing on plant foods rich in specific bioactive compounds could contribute to alleviating the dramatic burden of metabolic and cardiovascular diseases.

**Sodium**

**Dietary Salt Promotes Cognitive Impairment Through Tau Phosphorylation**


**Significance:** The findings from this study identify a causal link between dietary salt, endothelial dysfunction, and tau pathology; accumulation of hyperphosphorylated tau is a hallmark of Alzheimer’s pathology.

Dietary habits and vascular risk factors promote both Alzheimer’s disease and cognitive impairment caused by vascular factors. Furthermore, accumulation of hyperphosphorylated tau, a microtubule-associated protein and a hallmark of Alzheimer’s pathology, is also linked to vascular cognitive impairment. In mice, a salt-rich diet leads to cognitive dysfunction associated with a nitric oxide deficit in cerebral endothelial cells and cerebral hypoperfusion. Here we report that dietary salt induces hyperphosphorylation of tau followed by cognitive dysfunction in mice, and that these effects are prevented by restoring endothelial nitric oxide production. The nitric oxide deficiency reduces neuronal calpain nitrosylation and results in enzyme activation, which, in turn, leads to tau phosphorylation by activating cyclin-dependent kinase 5. Salt-induced cognitive impairment is not observed in tau-null mice or in mice treated with anti-tau antibodies, despite persistent cerebral hypoperfusion and neurovascular dysfunction. These findings identify a causal link between dietary salt, endothelial dysfunction and tau pathology, independent of haemodynamic insufficiency. Avoidance of excessive salt intake and maintenance of vascular health may help to stave off the vascular and neurodegenerative pathologies that underlie dementia in the elderly.

**Gut Microbiome**

**Dietary Habits of 2- to 9-Year-Old American Children Are Associated With Gut Microbiome Composition**


**Significance:** The findings from this study link quantitative dietary intake with microbiome features in a diverse population of children consuming a predominantly Western diet.

**Background:** The human gut microbiome is recognized as an important determinant of human health, yet little is known about how dietary habits are related to the microbiome in post-weaned, pre-pubescent children. **Objective:** The goal of this work was to link quantitative dietary intake with microbiome features in a diverse population of children consuming a predominantly Western diet. **Design:** This was a cross-sectional study. **Participants/settings:** English- or Spanish-speaking families with healthy children between the ages of 2 and 9 years were recruited from a community-based, early childhood learning center in suburban Los Angeles, California between June and September 2014. Main outcome measures: Children included in the analyses (n=75) contributed three fecal samples and three quantitative 24-hour dietary recalls using the multiple-pass method with an average of 5.7 days between samples. Microbial communities of each fecal sample were characterized using Illumina sequencing of the 16S ribosomal RNA gene. Dietary recalls were analyzed using the Automated Self-Administered 24-Hour Recall Dietary Assessment Tool. **Statistical analysis performed:** Associations between dietary factors and microbiome features were assessed using the Kruskal-Wallis test, Spearman rank correlations, or permutational multivariate analysis of variance. For demographic and health-related variables, χ2 analyses were used to test for differences between age groups for categorical variables. **Results:** Our results show that age is correlated with three metrics of microbiome diversity (P<0.05) and is associated with both community structure (P=0.0488) and membership (P=0.0002). Several dietary food groups and nutrients were likewise associated with microbiome features. For example, consumption of non–whole-grain foods was associated with community structure (P=0.0089) and membership (P=0.0057), but not diversity (P>0.05). Likewise, the relative abundance of several bacterial taxa were linked to consumption of particular food groups and/or nutrients, as illustrated by the positive associations between total fruit (P<0.05) and fiber (P<0.05) consumption with the relative abundance of the *Lachnospira* genera. **Conclusions:** This hypothesis-generating study demonstrates that the composition of the child gut microbiome remains dynamic beyond the age of 3 years and responds to dietary differences across individuals. In particular, non–whole-grain foods fortified with vitamins and minerals appear to be associated with the composition of the microbiome. Future interventional or model organism-based studies will be needed to test these associations between diet and microbiome composition.