Best (But Oft-Forgotten) Practices: Identifying and Accounting for Regression to the Mean in Nutrition and Obesity Research


Significance: Failing to account for regression to the mean in statistical analyses of repeated measurements can lead to incorrect conclusions. Best practices and methods for quantifying regression to the mean are presented.

Background: Regression to the mean (RTM) is a statistical phenomenon where initial measurements of a variable in a nonrandom sample at the extreme ends of a distribution tend to be closer to the mean upon a second measurement. Unfortunately, failing to account for the effects of RTM can lead to incorrect conclusions on the observed mean difference between the 2 repeated measurements in a nonrandom sample that is preferentially selected for deviating from the population mean of the measured variable in a particular direction. Study designs that are susceptible to misattributing RTM as intervention effects have been prevalent in nutrition and obesity research. This field often conducts secondary analyses of existing intervention data or evaluates intervention effects in those most at risk (i.e., those with observations at the extreme ends of a distribution).

Objectives: To provide best practices to avoid unsubstantiated conclusions as a result of ignoring RTM in nutrition and obesity research.

Methods: We outlined best practices for identifying whether RTM is likely to be leading to biased inferences, using a flowchart that is available as a web-based app at https://dustytturner.shinyapps.io/DecisionTreeMeanRegression/. We also provided multiple methods to quantify the degree of RTM.

Results: Investigators can adjust analyses to include the RTM effect, thereby plausibly removing its biasing influence on estimating the true intervention effect.

Conclusions: The identification of RTM and implementation of proper statistical practices will help advance the field by improving scientific rigor and the accuracy of conclusions. This trial was registered at clinicaltrials.gov as NCT00427193.

Best Practices for Conducting and Interpreting Studies to Validate Self-Report Dietary Assessment Methods


Significance: Challenges and a checklist of best practices related to the validation of self-report dietary assessment methods are presented.

Careful consideration of the validity and reliability of methods intended to assess dietary intake is central to the robustness of nutrition research. A dietary assessment method with high validity is capable of providing useful measurement for a given purpose and context. More specifically, a method with high validity is well grounded in theory; its performance is consistent with that theory; and it is precise, dependable, and accurate within specified performance standards. Assessing the extent to which dietary assessment methods possess these characteristics can be difficult due to the complexity of dietary intake, as well as difficulties capturing true intake. We identified challenges and best practices related to the validation of self-report dietary assessment methods. The term validation is used to encompass various dimensions that must be assessed and considered to determine whether a given method is suitable for a specific purpose. Evidence on the varied concepts of validity and reliability should be interpreted in combination to inform judgments about the suitability of a method for a specified purpose. Self-report methods are the focus because they are used in most studies seeking to measure dietary intake. Biomarkers are important reference measures to validate self-report methods and are also discussed. A checklist is proposed to contribute to strengthening the literature on the validation of dietary assessment methods and ultimately, the nutrition literature more broadly.
Dietary Patterns

Adherence to the Healthy Eating Index–2015 and Other Dietary Patterns May Reduce Risk of Cardiovascular Disease, Cardiovascular Mortality, and All-Cause Mortality

Significance: Protective associations were found between adherence to the Healthy Eating Index–2015, along with three other diet patterns, and risk of incident CVD, CVD mortality, and all-cause mortality.

Background: The Healthy Eating Index–2015 (HEI-2015) score measures adherence to recommendations from the 2015–2020 Dietary Guidelines for Americans. The HEI-2015 was altered from the HEI-2010 by reclassifying sources of dietary protein and replacing the empty calories component with 2 new components: saturated fats and added sugars. Objectives: Our aim was to assess whether the HEI-2015 score, along with 3 other previously defined indices, were associated with incident cardiovascular disease (CVD), CVD mortality, and all-cause mortality. Methods: We conducted a prospective analysis of 12,413 participants aged 45–64 y (56% women) from the Atherosclerosis Risk in Communities (ARIC) Study. The HEI-2015, Alternative Healthy Eating Index–2010 (AHEI-2010), alternate Mediterranean (aMed) diet, and Dietary Approaches to Stop Hypertension Trial (DASH) scores were computed using the average dietary intakes of Visits 1 (1987–1989) and 3 (1993–1995). Incident CVD, CVD mortality, and all-cause mortality data were ascertained from baseline through 31 December, 2017. We used Cox proportional hazards models to estimate HRs and 95% CIs. Results: There were 4509 cases of incident CVD, 1722 cases of CVD mortality, and 5747 cases of all-cause mortality over a median of 24–25 y of follow-up. Compared with participants in the lowest quintile of HEI-2015, participants in the highest quintile had a 16% lower risk of incident CVD (HR: 0.84; 95% CI: 0.76–0.93; P-trend < 0.001), 32% lower risk of CVD mortality (HR: 0.68; 95% CI: 0.58–0.80; P-trend < 0.001), and 18% lower risk of all-cause mortality (HR: 0.82; 95% CI: 0.75–0.89; P-trend < 0.001) after adjusting for demographic and lifestyle covariates. There were similar protective associations for AHEI-2010, aMed, and DASH scores, and no significant interactions by race. Conclusions: Higher adherence to the 2015–2020 Dietary Guidelines for Americans was associated with lower risks of incident CVD, CVD mortality, and all-cause mortality among US adults.

Protein

Amount Rather than Animal vs Plant Protein Intake Is Associated With Skeletal Muscle Mass in Community-Dwelling Middle-Aged and Older Chinese Adults: Results From the Guangzhou Nutrition and Health Study

Significance: In community-dwelling middle-aged and older Chinese adults, higher dietary intakes of protein (regardless of the ratio of animal-to-plant protein) are associated with greater skeletal muscle mass.

Background: Current literature does not indicate if the amount and animal vs plant protein are equally important in the prevention of muscle loss in middle-aged and older Chinese adults. Objective: The aim of the study was to examine the associations between amount or animal vs plant protein and skeletal muscle mass in Chinese adults aged 40 to 80 years. Design: A cross-sectional analysis of a prospective, community-based cohort was performed. Participants/setting: Participants included 1,044 men and 2,169 women aged 40 to 80 years from the Guangzhou Nutrition and Health Study 2011-2013 with body composition measurements by dual-energy x-ray absorptiometry. Main outcome measure: The skeletal muscle index (SMI) was defined as appendicular skeletal muscle mass divided by body weight. Participants in the lowest quartile of the sex-specific SMI were considered to have low muscle mass (LMM). Statistical analysis: Analyses of covariance were performed to estimate the SMI across quintiles of relative dietary intake of total, animal, and plant protein and the ratio of animal-to-plant protein. Logistic regression models were applied to assess the associations between quintiles of protein intake and LMM. Results: The SMI increased significantly across quintiles of relative dietary intake of total, animal, and plant protein (all P trends<0.001). Odds ratios (95% CIs) for LMM among participants in the highest (vs lowest) quintile were 0.3 (0.2, 0.4) for total protein, 0.3 (0.2, 0.5) for animal protein, and 0.4 (0.3, 0.7) for plant protein, respectively (all P trends<0.001). However, the ratio of animal-to-plant protein was not associated with either the SMI or the presence of LMM. Conclusion: Higher dietary intakes of total, animal, and plant protein, regardless of the ratio of animal-to-plant protein, are associated with greater skeletal muscle mass in community-dwelling middle-aged and older Chinese adults with a mean protein intake above the current recommendation for protein of 0.8 g/kg per day.
Lipids

EPA and DHA Have Divergent Effects on Serum Triglycerides and Lipogenesis, But Similar Effects on Lipoprotein Lipase Activity: A Randomized Controlled Trial

Significance: Concomitant increases in lipogenesis and LPL activity may explain the null effect of EPA supplementation on blood triglycerides.

Background: Comparative studies suggest that DHA may have stronger serum triglyceride–lowering effects than EPA; however, the molecular basis for this differential effect remains unexplored in humans. Differential regulation of lipogenesis and triglyceride clearance are 2 possible mechanisms of action. Objectives: We compared the effects of EPA and DHA supplementation on serum triglycerides, markers of lipogenesis, and lipoprotein lipase (LPL) activity in adults participating in a double-blind, multiarm, placebo-controlled parallel-group randomized trial. Lipogenesis was assessed with the lipogenic index and compound specific isotope analysis (CSIA). Methods: Young, healthy normolipidemic men and women (n = 89; 21.6 ± 0.23 y; mean ± SEM) were randomly allocated into 1 of 3 supplement groups for 12 wk: 1) olive oil, 2) ~3 g EPA/d, and 3) ~3 g DHA/d. Omega-3 supplements were provided in triglyceride form. Blood was collected before and after supplementation for the analysis of fatty acids and preheparin LPL activity. Variations in the 13C:12C ratio (δ13C) of palmitate (16:0) and linoleate (18:2n–6) were measured by CSIA. Results: DHA supplementation reduced blood triglycerides (0.85 ± 0.04 mmol/L to 0.65 ± 0.03 mmol/L; P < 0.01), with no change seen with EPA supplementation. DHA supplementation did not change the lipogenic index or δ13C-16:0, whereas EPA supplementation increased the lipogenic index by 11% (P < 0.01) and δ13C-16:0 (P = 0.03) from −23.2 ± 0.2 to −22.8 ± 0.2 milliUrey ± SEM. Conclusions: Reduced triglyceride concentrations after DHA supplementation are associated with increased LPL activity, whereas the null effect of EPA supplementation on blood triglycerides may stem from the concomitant increases in lipogenesis and LPL activity. Further investigation of the differential triglyceride-lowering effects of EPA and DHA is warranted in both normolipidemic and hyperlipidemic individuals. This trial was registered at clinicaltrials.gov as NCT03378232.

Carbohydrates

The Role of Dietary Sugars in Health: Molecular Composition or Just Calories?

Significance: The findings from this review do not support the conclusion that dietary sugars per se are detrimental to human health.

This review will focus on the question of whether dietary sugars are a relevant determinant in the global rise of overweight and obesity in adults, adolescents, and children. Initially, the review describes the current definitions for sugars in the diet and makes reference to them while analyzing their role in overweight and obesity as well as diet-related diseases, including type 2 diabetes, cardiovascular diseases, non-alcoholic fatty liver disease and cancer. Second, it will focus particularly on sucrose and the question of whether it is the molecular composition of sucrose (glucose and fructose) or its energy content that promotes body weight gain and diet-related diseases. Finally, the review will clarify the molecular characteristics of sucrose regarding the release of the gastrointestinal glucose-dependent insulinotropic peptide (GIP) compared to other energy-providing nutrients and its relevance in metabolic diseases. Current data indicates that dietary sugars are only associated with an increase in obesity when consumed as an excess source of calories and with that an increase in the risk of diet-related diseases. Furthermore, it was shown that a diet rich in fat will stimulate GIP secretion more than a diet rich in sucrose. Taken together, current scientific evidence does not support the conclusion that dietary sugars per se are detrimental to human health.

Low-Calorie Sweeteners

Cumulative Intake of Artificially Sweetened and Sugar-Sweetened Beverages and Risk of Incident Type 2 Diabetes in Young Adults: The Coronary Artery Risk Development In Young Adults (CARDIA) Study

Significance: A prospective analysis of young adults found that long-term artificially sweetened beverage (ASB) and sugar-sweetened beverage consumption were associated with increased risks of type 2 diabetes; however, estimates for ASB were attenuated when accounting for weight changes.

Background: Epidemiological evidence has demonstrated a positive association between artificially sweetened beverage (ASB) and sugar-sweetened beverage (SSB) consumption and type 2 diabetes (T2D) risk. However, research informing this topic in...
young adults is limited. **Objective:** This study examined the association between ASB, SSB, and total sweetened beverage (TSB; combined ASB and SSB) consumption and T2D risk in young adults. **Methods:** A prospective analysis of 4719 Black and White men and women aged 18–30 y at baseline was conducted from the Coronary Artery Risk Development in Young Adults (CARDIA) study. Each participant’s beverage intake was assessed using the CARDIA Diet History at baseline and at study Years 7 and 20. Multivariable Cox proportional hazards regression models were used to examine cumulative average ASB, SSB, and TSB intakes and risk of T2D. **Results:** During the 30-y follow-up period, 680 participants developed T2D. ASB consumption was associated with a 12% greater risk of T2D per serving/day (HR 1.12, 95% CI 1.04–1.20) in a model adjusted for lifestyle factors, diet quality, and dieting behavior. Further adjustments for baseline BMI (HR 1.07, 95% CI 0.99–1.14) and weight change during follow-up (HR 1.04, 95% CI 0.97–1.12) attenuated the association. SSB and TSB consumption as continuous variables per 1 serving/day of intake were associated with 6% and 5% increased risks of T2D, respectively (HRSSB 1.06, 95% CI 1.01–1.10; HRTSB 1.05, 95% CI 1.01–1.09), in the model accounting for lifestyle factors, dieting behavior, baseline BMI, and weight change. Results were consistent when the exposures were modeled in categories of consumption and quintiles. **Conclusions:** In young adults, long-term ASB, SSB, and TSB consumption were associated with increased risks of T2D. However, the estimates for ASB were attenuated when accounting for weight changes.

**Bioactives**

**A Systematic Review and Meta-Analysis of Randomized Controlled Trials on the Effects of Turmeric and Curcuminoids on Blood Lipids in Adults with Metabolic Diseases**


**Significance:** This systematic review and meta-analysis found evidence to support a lowering effect of turmeric and curcuminoids on blood triglycerides, total cholesterol, and LDL cholesterol. However, heterogeneity was high between included studies.

Dyslipidemia is a global health problem and a high risk factor for atherosclerosis, which can lead to serious cardiovascular disease (CVD). Existing studies have shown inconsistent effects of turmeric and curcuminoids on blood lipids in adults. We performed this systematic review and meta-analysis to evaluate the effects of turmeric and curcuminoids on blood triglycerides (TG), total cholesterol (TC), LDL cholesterol, and HDL cholesterol. We searched the English databases of the Web of Science, PubMed, Ovid (including EMBASE and MEDLINE), Scopus, and the Cochrane Library and 2 Chinese databases, Wanfang Data and China National Knowledge Infrastructure, for randomized controlled trials (RCTs) that studied the effects of turmeric and curcuminoids on blood TG, TC, LDL cholesterol, and HDL cholesterol in subjects with metabolic diseases. With random-effects models, separate meta-analyses were conducted by using inverse-variance. The results are presented as the mean difference with 95% CIs. Evidence from 12 RCTs for TG, 14 RCTs for TC, 13 RCTs for LDL cholesterol, and 16 RCTs for HDL cholesterol showed that turmeric and curcuminoids could lower blood TG by -19.1 mg/dL (95% CI: -31.7, -6.46 mg/dL; P = 0.003), TC by -11.4 mg/dL (95% CI: -17.1, -5.74 mg/dL; P < 0.0001), and LDL cholesterol by -9.83 mg/dL (95% CI: -15.9, -3.74 mg/dL; P = 0.002), and increase HDL cholesterol by 1.9 mg/dL (95% CI: 0.31, 3.49 mg/dL; P = 0.02). In conclusion, turmeric and curcuminoids can significantly modulate blood lipids in adults with metabolic diseases. However, these findings should be interpreted cautiously because of the significant heterogeneity between included studies (I² > 50%). There is a need for further RCTs in future.

**Sodium**

**Self-Reported Measures of Discretionary Salt Use Accurately Estimated Sodium Intake Overall But Not in Certain Subgroups of US Adults From 3 Geographic Regions in the Salt Sources Study**


**Significance:** The Healthy People 2020 methodology for estimating sodium consumed from salt added at the table underestimates intake in certain population subgroups.

**Background:** Excess sodium intake can increase blood pressure, and high blood pressure is a major risk factor for cardiovascular disease. Accurate population sodium intake estimates are essential for monitoring progress toward reduction, but data are limited on the amount of sodium consumed from discretionary salt. **Objectives:** The aim of this study was to compare measured sodium intake from salt added at the table with that estimated according to the Healthy People 2020 (HP 2020) methodology. **Methods:** Data were analyzed from the 2014 Salt Sources Study, a cross-sectional convenience sample of 450 white, black,
Asian, and Hispanic adults living in Alabama, Minnesota, and California. Sodium intake from foods and beverages was assessed for each participant through the use of 24-h dietary recalls. Estimated sodium intake from salt used at the table was assessed from self-reported frequency and estimated amounts from a previous study (HP 2020 methodology). Measured intake was assessed through the use of duplicate salt samples collected on recall days. Results: Among all study participants, estimated and measured mean sodium intakes from salt added at the table were similar, with a nonsignificant difference of 8.9 mg/d (95% CI: −36.6, 54.4 mg/d). Among participants who were non-Hispanic Asian, Hispanic, had a bachelor’s degree or higher education, lived in California or Minnesota, did not report hypertension, or had normal BMI, estimated mean sodium intake was 77–153 mg/d greater than measured intake (P < 0.05). The estimated mean sodium intake was 186–300 mg/d lower than measured intake among participants who were non-Hispanic black, had a high school degree or less, or reported hypertension (P < 0.05). Conclusions: The HP 2020 methodology for estimating sodium consumed from salt added at the table may be appropriate for the general US adult population; however, it underestimates intake in certain population subgroups, particularly non-Hispanic black, those with a high school degree or less, or those with self-reported hypertension. This study was registered at clinicaltrials.gov as NCT02474693.

**Gut Microbiome**

**Dietary Quality and the Colonic Mucosa–Associated Gut Microbiome in Humans**


**Significance:** A lower Healthy Eating Index–2005 score was associated with reduced relative abundance of potentially beneficial bacteria and increased potentially harmful bacteria in the colonic mucosa of endoscopically normal individuals.

**Background:** Despite tremendous interest in modulating the microbiome to improve health, the association between diet and the colonic mucosa–associated gut microbiome in healthy individuals has not been examined. **Objective:** To investigate the associations between Healthy Eating Index (HEI)–2005 and the colonic mucosa–associated microbiota. **Methods:** In this cross-sectional observational study, we analyzed bacterial community composition and structure using 16S rRNA gene (V4 region) sequencing of 97 colonic mucosal biopsies obtained endoscopically from different colon segments of 34 polyp-free participants. Dietary consumption was ascertained using an FFQ. Differences in α- and β-diversity and taxonomic relative abundances between the higher and lower score of total HEI and its components were compared, followed by multivariable analyses. **Results:** The structure of the microbiota significantly differed by the scores for total HEI, total and whole fruits (HEI 1 and HEI 2), whole grains (HEI 6), milk products and soy beverages (HEI 7), and solid fat, alcohol, and added sugar (HEI 12). A lower score for total HEI and HEIs 2, 7, and 12 was associated with significantly lower richness. A lower score for total HEI was associated with significantly reduced relative abundance of Parabacteroides, Roseburia, and Subdoligranulum but higher Fusobacterium. A lower score for HEI 2 was associated with lower Roseburia but higher Bacteroides. A lower score for HEI 7 was associated with lower Faecalibacterium and Fusobacterium but higher Bacteroides. A lower score for HEI 12 was associated with lower Subdoligranulum but higher Escherichia and Fusobacterium (false discovery rate–adjusted P values <0.05). The findings were confirmed by multivariate analysis. Less abundant bacteria such as Alistipes, Odoribacter, Bilophila, and Tyzzerella were also associated with dietary quality. **Conclusions:** A lower score for total HEI–2005 was significantly associated with reduced relative abundance of potentially beneficial bacteria but increased potentially harmful bacteria in the colonic mucosa of endoscopically normal individuals.

**Effects of Single and Combined Toxic Exposures on the Gut Microbiome: Current Knowledge and Future Directions**


**Significance:** This report identifies studies that are needed to comprehensively evaluate the effects of chemical pollutants and food additives on the gut microbiome.

Human populations are chronically exposed to mixtures of toxic chemicals. Predicting the health effects of these mixtures requires a large amount of information on the mode of action of their components. Xenobiotic metabolism by bacteria inhabiting the gastrointestinal tract has a major influence on human health. Our review aims to explore the literature for studies looking to characterize the different modes of action and outcomes of major chemical pollutants, and some components of cosmetics and food additives, on gut microbial communities in order to facilitate an estimation of their potential mixture effects. We identified good evidence that exposure to heavy metals, pesticides, nanoparticles, polycyclic aromatic hydrocarbons, dioxins, furans, polychlorinated biphenyls, and non-caloric artificial sweeteners affect the gut microbiome and which is associated with the development of metabolic, malignant, inflammatory, or immune diseases. Answering the question ‘Who is there?’ is not sufficient to define the mode of action of a toxicant in predictive modeling of mixture effects. Therefore, we recommend that new studies focus to simulate real-life exposure to diverse chemicals (toxicants, cosmetic/food additives), including as mixtures, and which combine metagenomics, metatranscriptomics and metabolomic analytical methods achieving in that way a comprehensive evaluation of effects on human health.