Dietary Patterns

Diet-Quality Indexes Are Associated with a Lower Risk of Cardiovascular, Respiratory, and All-Cause Mortality among Chinese Adults


Significance: Adherence to plant-based dietary patterns is associated with reduced risk of chronic disease mortality in an Asian population.

Background: Diet-quality indexes have been associated with a lower risk of chronic disease mortality in Western populations, but it is unclear whether these indexes reflect protective dietary patterns in Asian populations. Objective: We examined the association between Alternative Healthy Eating Index-2010 (AHEI-2010), alternate Mediterranean diet (aMED), Dietary Approaches to Stop Hypertension (DASH), and Healthy Diet Indicator (HDI) scores and the risk of all-cause cardiovascular disease (CVD), cancer, and respiratory disease mortality. Methods: We used data from a prospective cohort of 57,078 Singapore Chinese men and women (aged 45-74 y) who were free of cancer and CVD at baseline (1993-1998) and who were followed up through 2014. The diet-quality index scores were calculated on the basis of data from a validated 165-item food-frequency questionnaire. Cox regression models with adjustment for potential confounders including sociodemographic and lifestyle variables, body mass index, and medical history were used to estimate HRs and 95% CIs. Results: During a total of 981,980 person-years of follow-up, 15,262 deaths (CVD: 4871; respiratory: 2690; and cancer: 5306) occurred. Comparing the highest with the lowest quintiles, the multivariable adjusted HRs (95% CIs) for all-cause mortality were 0.82 (0.78, 0.86) for AHEI-2010, 0.80 (0.76, 0.85) for aMED, 0.80 (0.75, 0.84) for DASH, and 0.88 (0.83, 0.92) for HDI scores (all P-trend < 0.001). Higher diet index scores were associated with a 14-28% lower risk of CVD and respiratory mortality, but only a 5-12% lower risk of cancer mortality. Higher consumption of vegetables, fruit, nuts, and long-chain n-3 (ω-3) fatty acids, lower consumption of red meat, and avoidance of high alcohol consumption were the diet index components associated with a lower risk of mortality. Conclusion: Adherence to several recommended dietary patterns that emphasize healthy plant-based foods was associated with a substantially lower risk of chronic disease mortality in an Asian population. The Singapore Chinese Health Study was registered at www.clinicaltrials.gov as NCT03356340.

Effects of Low-Carbohydrate- Compared with Low-Fat-Diet Interventions on Metabolic Control in People with Type 2 Diabetes: A Systematic Review Including GRADE Assessments


Significance: This systematic review found low- to moderate-quality evidence that dietary carbohydrate restriction may yield better metabolic control than fat restriction in individuals with type 2 diabetes.

Background: It remains uncertain which diet is best for people with type 2 diabetes (T2D). Objective: We compared the effects of dietary carbohydrate restriction with fat restriction on markers of metabolic syndrome and quality of life in people with T2D. Design: This systematic review of randomized controlled trials (RCTs) and controlled clinical trials (CCTs) compares the effects of a low-carbohydrate [≤40% of energy (%)] diet with those of a low-fat (≤30%) diet over a period of ≥4 wk in patients with T2D. Two investigators independently selected studies, extracted data, and assessed risk of bias. The GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach was used to assess the certainty of evidence. Pooled mean differences (MDs) and 95% CIs were calculated with the use of a random-effects model. Results: Thirty-three RCTs and 3 CCTs (n = 2161) were included. Glycated hemoglobin declined more in people who consumed low-carbohydrate food than in those who consumed low-fat food in the short term (MD: -1.38%; 95% CI: -2.64%, -0.11%; very-low-certainty evidence). At 1 y, the MD was reduced to -0.36% (95% CI: -0.58%, -0.14%; low-certainty evidence); at 2 y, the difference had disappeared. There is low to high (majority moderate) certainty for small improvements of unclear clinical importance in plasma glucose, triglycerides, and HDL concentrations favoring low-carbohydrate food at half of the prespecified time points. There was little to no difference in LDL concentration or any of the secondary outcomes (body weight, waist circumference, blood pressure, quality of life) in response to either of the diets (very-low- to high-certainty evidence). Conclusions: Currently available data provide
low- to moderate-certainty evidence that dietary carbohydrate restriction to a maximum of 40% yields slightly better metabolic control of uncertain clinical importance than reduction in fat to a maximum of 30% in people with T2D. This systematic review is registered at http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017052467 as CRD42017052467.

**Protein**

**Plasma Concentrations of Anserine, Carnosine and Pi-methylhistidine as Biomarkers of Habitual Meat Consumption**


**Significance:** This cross-sectional study suggests that plasma concentrations of anserine, carnosine, Π-MH may serve as biomarkers of meat, poultry, fish and dairy intake.

**Background/Objectives:** Dietary intake of red and processed meat has been associated with disease risk. Since dietary intake assessment methods are prone to measurement errors, identifying biomarkers of meat intake in bio-samples could provide more valid intake estimates. We examined associations of habitual red and processed meat, poultry, fish, and dairy products consumption with plasma concentrations of anserine, carnosine, pi-methylhistidine (Π-MH), tau-methylhistidine (T-MH), and the ratio of T-MH to Π-MH in a cross-sectional study. **Subjects/Methods:** Plasma anserine, carnosine, Π-MH, and T-MH concentrations were measured using ion-pair LC-MS/MS in 294 participants in the second Bavarian Food Consumption Survey (BVS II). Habitual food consumption was assessed using three 24-h dietary recalls. Associations between plasma metabolites concentrations and meat, fish, eggs, and dairy products consumption were assessed by fitting generalized linear model, adjusted for age, sex, and BMI. **Results:** Total meat intake was associated with plasma concentrations of anserine, carnosine, Π-MH and, the ratio of T-MH to Π-MH. Red meat intake was related to carnosine (p-trend = 0.0028) and Π-MH plasma levels (p-trend = 0.0493). Poultry (p-trend = 0.0006) and chicken (p-trend = 0.0003) intake were associated with Π-MH. The highest anserine concentrations were observed in individuals consuming processed meat or turkey. For T-MH we did not observe any association with meat intake. **Conclusions:** Our results indicate an association between habitual meat consumption and plasma concentrations of anserine, carnosine, Π-MH and the ratio of T-MH to Π-MH. Intervention studies should clarify whether the analyzed plasma metabolites are indicative for a specific type of meat before proposing them as biomarkers of habitual meat intake in epidemiologic studies.

**A Systematic Review of Renal Health in Healthy Individuals Associated with Protein Intake above the US Recommended Daily Allowance in Randomized Controlled Trials and Observational Studies**


**Significance:** Currently available data are insufficient to determine if increased protein intake from a specific source (i.e. plant or animal) influences kidney health outcomes.

A systematic review was used to identify randomized controlled trials (RCTs) and observational epidemiologic studies (OBSs) that examined protein intake consistent with either the US RDA (0.8 g/kg or 10-15% of energy) or a higher protein intake (≥20% but <35% of energy or ≥10% higher than a comparison intake) and reported measures of kidney function. Studies (n = 26) of healthy, free-living adults (>18 y old) with or without metabolic disease risk factors were included. Studies of subjects with overt disease, such as chronic kidney, end-stage renal disease, cancer, or organ transplant, were excluded. The most commonly reported variable was glomerular filtration rate (GFR), with 13 RCTs comparing GFRs obtained with normal and higher protein intakes. Most (n = 8), but not all (n = 5), RCTs reported significantly higher GFRs in response to increased protein intake, and all rates were consistent with normal kidney function in healthy adults. The evidence from the current review is limited and inconsistent with regard to the role of protein intake and the risk of kidney stones. Increased protein intake had little or no effect on blood markers of kidney function. Evidence reported here suggests that protein intake above the US RDA has no adverse effect on blood pressure. All included studies were of moderate to high risk of bias and, with the exception of 2 included cohorts, were limited in duration (i.e. <6 mo). Data in the current review are insufficient to determine if increased protein intake from a particular source, i.e., plant or animal, influences kidney health outcomes. These data further indicate that, at least in the short term, higher protein intake within the range of recommended intakes for protein is consistent with normal kidney function in healthy individuals.
Carbohydrates

Effect of 12 wk of Resistant Starch Supplementation on Cardiometabolic Risk Factors in Adults with Prediabetes: A Randomized Controlled Trial


Significance: Relative to rapidly digestible starch, supplementation with resistance starch did not improve glycemic control in adults with prediabetes.

Background: Type 2 resistant starch (RS2) has been shown to improve glycemic control and some cardiovascular endpoints in rodent and human studies. Objective: The aim of this study was to perform one of the first randomized clinical trials in adults with prediabetes and one of the longest trials to test whether RS2 can improve cardiometabolic health. Design: 68 overweight [body mass index (BMI) ≥27 kg/m²] adults aged 35-75 y with prediabetes were randomized to consume 45 g/d of high-amylose maize (RS2) or an isocaloric amount of the rapidly digestible starch amylopectin (control) for 12 wk. At baseline and postintervention, ectopic fat depots (visceral adipose tissue, intrahepatic lipids, and intramyocellular lipids) were measured by magnetic resonance imaging/spectroscopy, energy metabolism by respiratory chamber, and carbohydrate metabolism by glycated hemoglobin (HbA1c), an intravenous glucose tolerance test, and a meal tolerance test. Cardiovascular risk factors—serum lipids, blood pressure, heart rate, and inflammatory markers (high-sensitivity C-reactive protein [hs-CRP], interleukin-6, and tumor necrosis factor [TNF]-α)—were also measured. The primary endpoints were insulin sensitivity, insulin secretion, ectopic fat, and markers of inflammation. Data were primarily analyzed as treatment effects via a linear mixed model both with and without the addition of covariates. Results: Relative to the control group, RS2 lowered HbA1c by a clinically insignificant 0.1 ± 0.2% (Δ = -1 ± 2 mmol/mol; P = 0.05) but did not affect insulin secretion, insulin sensitivity, the disposition index, or glucose or insulin areas under the curve relative to baseline (P ≥ 0.23). RS2 decreased heart rate by 5 ± 9 beats/min (P = 0.02) and TNF-α concentrations by 2.1 ± 2.7 pg/mL (P = 0.004), relative to the control group. Ectopic fat, energy expenditure, substrate oxidation, and all other cardiovascular risk factors were unaffected (P ≥ 0.06). Conclusions: 12 wk of supplementation with resistant starch reduced the inflammatory marker TNF-α and heart rate, but it did not significantly improve glycemic control and other cardiovascular disease risk factors, in adults with prediabetes. This trial was registered at clinicaltrials.gov as NCT01708694.

Higher Whole-Grain Intake Is Associated with Lower Risk of Type 2 Diabetes among Middle-Aged Men and Women: The Danish Diet, Cancer, and Health Cohort


Significance: The associations between intakes of different grain and cereal products and risk of type 2 diabetes were examined.

Background: Type 2 diabetes is a major health concern worldwide. Whole grains and cereal fiber may offer protective effects on type 2 diabetes risk. However, few studies have been conducted in cohorts with detailed information on whole-grain cereal intakes and product types and with wide ranges of intake. Objective: We investigated the associations between whole-grain intake, including intakes of different cereal types and products, and the risk of type 2 diabetes in a population with wide and diverse whole-grain intake. Methods: We used data from the Danish Diet, Cancer, and Health cohort including 55,465 participants aged 50-65 y at baseline. Of these, 7417 participants were diagnosed with type 2 diabetes during follow-up (median: 15 y). Detailed information on the intake of whole-grain products was available from a food-frequency questionnaire, and total whole-grain intake and whole-grain cereal types (wheat, rye, oats) were calculated in grams per day. Associations were examined by using Cox proportional hazards models with adjustment for potential confounders. Results: Whole-grain intake was associated with an 11% and 7% lower risk of type 2 diabetes per whole-grain serving (16 g) per day for men and women, respectively [HR (95% CI)—men: 0.89 (0.87, 0.91); women: 0.93 (0.91, 0.96)]. For men, the intake of all whole-grain cereal types investigated (wheat, rye, oats) was significantly associated with a lower risk of type 2 diabetes, but only wheat and oats intake was significantly associated for women. Among the different whole-grain products, rye bread, whole-grain bread, and oatmeal/muesli were significantly associated with a lower risk of type 2 diabetes for both men and women. Conclusions: In this cohort study, we found consistent associations between high whole-grain intake and lower risk of type 2 diabetes. Overall, an association was found for all different cereals and whole-grain products tested.
Low-Calorie Sweeteners

Hypotheses and Evidence Related to Intense Sweeteners and Effects on Appetite and Body Weight Changes: A Scoping Review of Reviews


Significance: This scoping review assessed the evidence on intense sweeteners’ potential relationships to appetite and weight changes.

Observed associations between consumption of diet foods and obesity have sparked controversy over whether intense sweeteners may promote weight gain, despite their negligible energy contribution. We conducted a scoping review of reviews, to obtain an overview of hypotheses, research approaches and features of the evidence on intense sweeteners’ potential relationships to appetite and weight changes. We searched for reviews of the scientific literature published from 2006 to May 2017. Two reviewers independently assessed title and abstracts, and full text publications. Arksey and O’Malley’s framework for scoping reviews guided the process. We extracted and charted data on characteristics of the reviews and the evidence presented. The 40 included reviews present hypotheses both on how intense sweeteners can reduce or maintain body weight and on how these can promote weight gain. We classified only five publications as systematic reviews; another nine presented some systematic approaches, while 26 reviews did not describe criteria for selecting or assessing the primary studies. Evidence was often presented for intense sweeteners as a group or unspecified, and against several comparators (e.g. sugar, water, placebo, intake levels) with limited discussion on the interpretation of different combinations. Apart from the observational studies, the presented primary evidence in humans is dominated by small studies with short follow-up-considered insufficient to assess weight change. Systematic reviews of animal studies are lacking in this topic area. The systematic evidence only partly explore forwards hypotheses found in the literature. Primary studies in humans seem to be available for systematic exploration of some hypotheses, but long-term experimental studies in humans appear sparse. With few exceptions, the reviews on intense sweeteners and weight change underuse systematic methodology, and thus, the available evidence. Further studies and systematic reviews should be explicit about the hypothesis explored and elucidate possible underlying mechanisms.

Low-Calorie Sweetened Beverages and Cardiometabolic Health


Significance: This advisory reviews evidence regarding the cardiometabolic outcomes of low-calorie sweeteners, and summarizes the positions of government agencies and other health organizations on low-calorie sweeteners.

In the United States, 32% of beverages consumed by adults and 19% of beverages consumed by children in 2007 to 2010 contained low-calorie sweeteners (LCSs). Among all foods and beverages containing LCSs, beverages represent the largest proportion of LCS consumption worldwide. The term LCS includes the 6 high-intensity sweeteners currently approved by the US Food and Drug Administration and 2 additional high-intensity sweeteners for which the US Food and Drug Administration has issued no objection letters. Because of a lack of data on specific LCSs, this advisory does not distinguish among these LCSs. Furthermore, the advisory does not address foods sweetened with LCSs. This advisory reviews evidence from observational studies and clinical trials assessing the cardiometabolic outcomes of LCS beverages. It summarizes the positions of government agencies and other health organizations on LCS beverages and identifies research needs on the effects of LCS beverages on energy balance and cardiometabolic health. The use of LCS beverages may be an effective strategy to help control energy intake and promote weight loss. Nonetheless, there is a dearth of evidence on the potential adverse effects of LCS beverages relative to potential benefits. On the basis of the available evidence, the writing group concluded that, at this time, it is prudent to advise against prolonged consumption of LCS beverages by children. (Although water is the optimal beverage choice, children with diabetes mellitus who consume a balanced diet and closely monitor their blood glucose may be able to prevent excessive glucose excursions by substituting LCS beverages for sugar-sweetened beverages [SSBs] when needed.) For adults who are habitually high consumers of SSBs, the writing group concluded that LCS beverages may be a useful replacement strategy to reduce intake of SSBs. This approach may be particularly helpful for persons who are habituated to a sweet-tasting beverage and for whom water, at least initially, is an undesirable option. Encouragingly, self-reported consumption of both SSBs and LCS beverages has been declining in the United States, suggesting that it is feasible to reduce SSB intake without necessarily substituting LCS beverages for SSBs. Thus, the use of other alternatives to SSBs, with a focus on water (plain, carbonated, and unsweetened flavored), should be encouraged.
Lipids

Plasma Metabolites and Lipids Predict Insulin Sensitivity Improvement in Obese, Nondiabetic Individuals after a 2-Phase Dietary Intervention


Significance: A model to predict insulin sensitivity improvement in overweight and obese individuals following a low-calorie diet was developed.

Background: Weight loss in obese individuals aims to reduce the risk of type 2 diabetes by improving glycemic control. Yet, significant intersubject variability is observed and the outcomes remain poorly predictable. Objective: The aim of the study was to predict whether an individual will show improvements in insulin sensitivity above or below the median population change at 6 mo after a low-calorie-diet (LCD) intervention. Design: With the use of plasma lipidomics and metabolomics for 433 subjects from the Diet, Obesity, and Genes (DiOGenes) Study, we attempted to predict good or poor Matsuda index improvements 6 mo after an 8-wk LCD intervention (800 kcal/d). Three independent analysis groups were defined: “training” (n = 119) for model construction, “testing” (n = 162) for model comparison, and “validation” (n = 152) to validate the final model. Results: Initial modeling with baseline clinical variables (body mass index, Matsuda index, total lipid concentrations, sex, age) showed limited performance [area under the curve (AUC) on the “testing dataset” = 0.69; 95% CI: 0.61, 0.77]. Significantly better performance was achieved with an omics model based on 27 variables (AUC = 0.77; 95% CI: 0.70, 0.85; P = 0.0297). This model could be greatly simplified while keeping the same performance. The simplified model relied on baseline Matsuda index, proline, and phosphatidylcholine 0:34:1. It successfully replicated on the validation set (AUC = 0.75; 95% CI: 0.67, 0.83) with the following characteristics: specificity = 0.73, sensitivity = 0.68, negative predictive value = 0.60, and positive predictive value = 0.80. Marginally lower performance was obtained when replacing the Matsuda index with homeostasis model assessment of insulin resistance (AUC = 0.72; 95% CI: 0.64, 0.80; P = 0.08). Conclusions: Our study proposes a model to predict insulin sensitivity improvements, 6 mo after LCD completion in a large population of overweight or obese nondiabetic subjects. It relies on baseline information from 3 variables, accessible from blood samples. This model may help clinicians assessing the large variability in dietary interventions and predict outcomes before an intervention. This trial was registered at www.clinicaltrials.gov as NCT00390637.

Serial Measures of Circulating Biomarkers of Dairy Fat and Total and Cause-Specific Mortality in Older Adults: The Cardiovascular Health Study


Significance: This prospective study evaluated the relationship between circulating biomarkers of dairy fat and cause-specific mortality and cardiovascular disease risk.

Background: Controversy has emerged about the benefits compared with harms of dairy fat, including concerns over long-term effects. Previous observational studies have assessed self-reported estimates of consumption or a single biomarker measure at baseline, which may lead to suboptimal estimation of true risk. Objective: The aim of this study was to investigate prospective associations of serial measures of plasma phospholipid fatty acids pentadecanoic (15:0), heptadecanoic (17:0), and trans-palmi-
toleic (trans-16:1n-7) acids with total mortality, cause-specific mortality, and cardiovascular disease (CVD) risk among older adults. Design: Among 2907 US adults aged ≥65 y and free of CVD at baseline, circulating fatty acid concentrations were measured serially at baseline, 6 y, and 13 y. Deaths and CVD events were assessed and adjudicated centrally. Prospective associations were assessed by multivariate-adjusted Cox models incorporating time-dependent exposures and covariates. Results: During 22 y of follow-up, 2428 deaths occurred, including 833 from CVD, 1595 from non-CVD causes, and 1301 incident CVD events. In multivariable models, circulating pentadecanoic, heptadecanoic, and trans-palmitoleic acids were not significantly associated with total mortality, with extreme-quintile HRs of 1.05 for pentadecanoic (95% CI: 0.91, 1.22), 1.07 for heptadecanoic (95% CI: 0.93, 1.23), and 1.05 for trans-palmi-
toleic (95% CI: 0.91, 1.20) acids. Circulating heptadecanoic acid was associated with lower CVD mortality (extreme-quintile HR: 0.77; 95% CI: 0.61, 0.98), especially stroke mortality, with a 42% lower risk when comparing extreme quintiles of heptadecanoic acid concentrations (HR: 0.58; 95% CI: 0.35, 0.97). In contrast, heptadecanoic acid was associated with a higher risk of non-CVD mortality (HR: 1.27; 95% CI: 1.07, 1.52), which was not clearly related to any single subtype of non-CVD death. No significant associations of pentadecanoic, heptadecanoic, or trans-palmitoleic acids were seen for total incident CVD, coronary heart disease, or stroke. Conclusions: Long-term exposure to circulating phospholipid pentadecanoic, heptadecanoic, or trans-palmitoleic acids was not significantly associated with total mortality or incident CVD among older adults. High circulating heptadecanoic acid was inversely associated with CVD and stroke mortality and potentially associated with higher risk of non-CVD death.
Association of Blood Levels of Marine Omega-3 Fatty Acids with Coronary Calcification and Calcium Density in Japanese Men


**Significance:** This cross-sectional study found that DHA but not EPA is inversely associated with coronary atherosclerosis in a Japanese population having high consumption of omega-3 fatty acids.

**Background/Objectives:** Clinical trials of eicosapentaenoic acid (EPA) among high-risk groups in Japan in which consumption of marine-omega-3 fatty acids (OM3) is much higher than other countries showed slower progression of coronary atherosclerosis. We aimed to determine the cross-sectional associations of coronary artery calcification (CAC) and calcium density with OM3, EPA, and docosahexaenoic acid (DHA), two principal OM3, in the general population in Japan. Subjects/Methods: The Shiga Epidemiological Study of Subclinical Atherosclerosis examined a population-based sample of 1074 men aged 40-79 in 2006-08 for computed tomography-measured CAC score (CCS), a well-established biomarker of coronary atherosclerosis, CAC density score (CDS), a potential marker of plaque stabilization, serum levels of OM3, and risk factors. Results: Prevalence of CCS > 0, ≥ 100, and ≥ 300 was 65.8%, 25.9%, and 12.9%, respectively; the mean (SD) OM3, EPA, and DHA were 10.1% (3.2), 3.2% (1.7), and 5.9% (1.6), respectively. Odds ratios (95% CI, p-value) of CCS 0, 100, and 300 in ordinal logistic regression associated with 1 SD increase of OM3, EPA, and DHA were 0.91 (0.81-1.03, p = 0.12), 0.99 (0.88-1.11, p = 0.87) and 0.84 (0.74-0.94, p < 0.01), respectively. The inverse association of DHA with CCS remained significant in multivariate-adjusted model: odds ratio of 0.87 (0.77-0.99, p = 0.03). Blood levels of OM3, EPA, or DHA did not have any significant associations with CDS. Conclusions: DHA but not EPA had a significant inverse association with coronary atherosclerosis in the general population with high levels of OM3. Future trials are warranted comparing the effect of high-dose DHA and EPA on atherosclerosis and cardiovascular outcomes.

Bioactives

Intrinsic and Extrinsic Factors Impacting Absorption, Metabolism, and Health Effects of Dietary Carotenoids


**Significance:** This paper discusses internal and external influences on blood serum and plasma carotenoid responses and highlights opportunities for future research to address knowledge gaps.

Carotenoids are orange, yellow, and red lipophilic pigments present in many fruit and vegetables, as well as other food groups. Some carotenoids contribute to vitamin A requirements. The consumption and blood concentrations of specific carotenoids have been associated with reduced risks of a number of chronic conditions. However, the interpretation of large, population-based observational and prospective clinical trials is often complicated by the many extrinsic and intrinsic factors that affect the physiologic response to carotenoids. Extrinsic factors affecting carotenoid bioavailability include food-based factors, such as co-consumed lipid, food processing, and molecular structure, as well as environmental factors, such as interactions with prescription drugs, smoking, or alcohol consumption. Intrinsic, physiologic factors associated with blood and tissue carotenoid concentrations include age, body composition, hormonal fluctuations, and variation in genes associated with carotenoid absorption and metabolism. To most effectively investigate carotenoid bioactivity and to utilize blood or tissue carotenoid concentrations as biomarkers of intake, investigators should either experimentally or statistically control for confounding variables affecting the bioavailability, tissue distribution, and metabolism of carotene and xanthophyll species. Although much remains to be investigated, recent advances have highlighted that lipid co-consumption, baseline vitamin A status, smoking, body mass and body fat distribution, and genetics are relevant covariates for interpreting blood serum or plasma carotenoid responses. These and other intrinsic and extrinsic factors are discussed, highlighting remaining gaps in knowledge and opportunities for future research. To provide context, we review the state of knowledge with regard to the prominent health effects of carotenoids.

Micronutrients

Are Serum Concentrations of Vitamin B-12 Causally Related to Cardiometabolic Risk Factors and Disease? A Mendelian Randomization Study


**Significance:** No causal relationships were found between serum concentrations of vitamin B-12 and body weight or most cardiometabolic outcomes, but vitamin B-12 may influence fasting glucose and HOMA-B.

**Background:** Several observational studies have shown that low serum vitamin B-12 is associated with increased body mass index (BMI) and adverse cardiometabolic outcomes. However, it is unclear if these associations reflect a causal effect of vitamin B-12
on cardiometabolic risk factors and diseases, latent confounding, or reverse causality. Objectives: The aims of this study were to investigate 1) the possible causal relation between vitamin B-12 and indicators of body fat, lipid, and glucose variables; type 2 diabetes (T2D); and cardiovascular disease by using a 2-sample Mendelian randomization (MR) method and 2) the possible pleiotropic role of fucosyltransferase 2 (FUT2). Design: We selected 11 single nucleotide polymorphisms (SNPs) robustly associated with serum concentrations of vitamin B-12 in a previous genomewide association study (GWAS) in 45,576 individuals. We performed 2-sample MR analyses of the relation between vitamin B-12 and cardiometabolic risk factors and diseases with the use of publicly available GWAS summary statistics for 15 outcomes in ≤339,224 individuals. The robustness of results was tested with sensitivity analyses by using MR Egger regression and weighted-median estimation, and by performing additional analyses excluding a variant in the FUT2 gene, which may be pleiotropic. Results: We found a suggestive causal relation between vitamin B-12 and fasting glucose and β cell function [homeostatic model assessment (HOMA) of β cell function (HOMA-B)]. However, we found no evidence that serum concentrations of vitamin B-12 were causally related to BMI, waist-to-hip ratio, plasma leptin, body fat, fasting insulin, insulin resistance (from HOMA of insulin resistance), glycated hemoglobin, triglycerides, T2D, coronary artery disease, or HDL, LDL, or total cholesterol. Conclusions: We found no evidence that serum concentrations of vitamin B-12 are causally related to body weight or the majority of cardiometabolic outcomes investigated. However, vitamin B-12 may have a causal effect on fasting glucose and HOMA-B, although these results will require replication in large independent data sets. This trial was registered at http://www.isrctn.com/ISRCTN47414943 as ISRCTN47414943.