SUNY Downstate Committee On
Plant-Based Health & Nutrition
More Plants, Less Meat, Better Health

SUNY Downstate Medical Center

Evidence Summary for Plant-Based Diets

Reviews, Trials, Large Cohort, and Landmark Observational Studies

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Definitions

- Omnivorous diet: includes animal and plant foods without any restrictions
- Plant-based diet: emphasizes eating more plant-based foods (i.e., fruits, vegetables, grains, nuts, seeds, and legumes/beans) and fewer or no animal products (i.e., red meat, poultry, fish, eggs, and dairy)
- Vegetarian diet: a plant-based diet that generally does not include meat, but may include eggs (ovo-vegetarian), dairy products (lacto-vegetarian), or both (lacto-ovo-vegetarian); some vegetarian diets also include fish (pescatarian), poultry or fowl (pollotarian)
- Semi-vegetarian diet: a vegetarian diet that excludes some types of meat (most often red meat), but may contain other types (e.g., poultry, fish)
- Flexitarian diet: a vegetarian-inclined diet that limits meat intake, but still includes meat
- Vegan diet: a more restrictive vegetarian diet that completely excludes animal products
- Whole-food, plant-based diet: a diet that emphasizes unrefined plants (such as whole grains), and avoids refined plant foods that have been processed and stripped of their nutrients (e.g., refined grains, added sugars, and extracted oils)

Note: There is increasing use of flexitarian diet and semi-vegetarian diet in the literature; the definitions here are adapted from Rosenfeld DL. The psychology of vegetarianism: recent advances and future directions. Appetite 2018; 131:125-38.

Motivations for Becoming Vegetarian

The 4 most common motivations people have for going vegetarian, in descending order of prevalence, include concerns related to the well-being of animals, their own health, the environment, and religion:

1. Animal rights/welfare – concern for the well-being of animals used for food, or the belief that using animals for food is unethical or immoral
2. Health – concern for one's own health, such as avoiding disease (e.g., heart disease, hypertension) or maintaining a healthy body weight
3. The environment – concern for the effects of meat (and other animal product) production on the environment (e.g., greenhouse gas emissions, water usage, pollution)
4. Religion – based on the rules of one's religious beliefs

Source: Rosenfeld DL. The psychology of vegetarianism: Recent advances and future directions. Appetite 2018; 131:125-38; and Ruby MB. Vegetarianism. A blossoming field of study. Appetite 2012; 58:141-150.

Another, more theoretical, motivation for becoming vegetarian relates to social identity, reflecting a desire to see oneself as vegetarian and to identify with this social category; a high social identity fosters belonging and helps makes sense of social environments.

Source: Plante CN, Rosenfeld DL, Plante M, Reysen S. The role of social identity motivation in dietary attitudes and behaviors among vegetarians. Appetite 2019; 141 https://doi.org/10.1016/j.appet.2019.05.038 [Epub ahead of print].

Plain Language Summary of Evidence

1. Research provides consistent evidence that plant-based diets offer significant benefits in promoting overall health and in preventing, managing, or treating many chronic diseases including excess weight, high blood pressure, coronary artery disease, high cholesterol, type 2 diabetes, and some cancers (colon, stomach, intestines, and prostrate).
2. The evidence is most supportive of increased consumption of whole (unrefined or minimally processed) plant foods as providing benefits, in contrast to reducing animal product in the diet, or removing them entirely; we improve health by *adding* whole plant foods not by simply cutting back on meat, dairy, or other animal products.
3. Within the category of plant-based diet there is some evidence to suggest that vegan diets provide benefits over other vegetarian diets. While there is little evidence that a whole-food plant-based diet is better than any other type of vegan diet, there is mounting evidence that eating whole plant foods is more beneficial than eating refined plant foods.
4. Some of the observed health benefits of plant-based diets may be due, in part, to other lifestyle patterns or interventions that often accompany these diets, such as smoking cessation, limited alcohol consumption, stress reduction, and a greater emphasis on exercise and fitness.
5. Current evidence on plant-based diets is based on people whose characteristics may differ from regions with a high prevalence of under-represented minorities, but the higher levels of obesity, diabetes, and other chronic diseases in these regions may accentuate the benefits of plant-based diets.

Executive Summary of Evidence

1. There is robust evidence on the impact of a plant-based diet on disease, mortality, and metabolic profiles based on large, population-based cohort studies that span several decades. These studies span the world and include (in order of decreasing sample size):
    a. UK Biobank Resource, N=500,000 enrolled 2006-2010
    b. Lifetime Risk Pooling Project, N=225,000 enrolled 1948-2010
    c. US Healthcare Worker Studies, N=200,727 enrolled in 3 studies: Nurses' Health Study 1984-2012, Nurses' Health Study 2 1991-2011, and the Health Professionals Follow-Up Study 1986-2012
    d. Seventh Day Adventist Studies, N=157,728 participants enrolled in 3 studies: 1960-66, 1976, and 2002-07
    e. Prospective Urban Rural Epidemiology (PURE) Study, N=135,335 enrolled from 2003-13
    f. The China Health and Nutrition Study, N=94,532 launched in 1989
    g. NurtiNet-Santé Study, N=93,823 web-based launched in 2009
    h. European Prospective Investigation into Cancer and Nutrition (EPIC) Study, N=65,429 enrolled in the 1990s
    i. US National Health and Nutrition Examination Survey, N=36,825 surveyed 1999-2014
    j. Singapore Chinese Health Study, N=63,257 enrolled 1993-98
    k. Prevention with Mediterranean Diet (PREDIMED) Study, N=7,216 enrolled from 2003-9
    l. Rotterdam Study, N=6,798 enrolled in 3 cohorts: 1989-93, 2000-01, and 2006-08
    m. The China Study, N=6,500, enrolled in 1983
    n. Tzu Chi Health Study (Taiwan), N=6,002 enrolled 2007-2009

2. Taken together, over 1,500,000 participants in large, population-based studies show lower rates of the following conditions associated with more plant foods in the diet:
    - ✓ Diseases: obesity, overweight, high body mass index (BMI), prediabetes, type 2 diabetes, high blood pressure, ischemic (coronary) heart disease, some cancers (gastrointestinal, colon), and metabolic syndrome (having at least 3 of the following 5 conditions: abdominal obesity, high blood pressure, high blood sugar, high serum triglycerides, and low HDL levels)
    - ✓ Mortality: deaths from all-causes, cardiovascular disease, ischemic heart disease, cerebrovascular disease, and some cancers (gastrointestinal, hematopoietic, lung, lymphatic, and pancreatic)

- ✓ Metabolic profiles: lower levels of total cholesterol, LDL cholesterol, non-HDL cholesterol, apolipoprotein B, glucose levels, hemoglobin A1c, insulin resistance, and obesity inflammatory profiles (CRP, IL-6, sICAM)
- ✓ Inadequate nutrition: not meeting nutritional recommendations (French NurtiNet-Santé Study)

3. One partial exception to the above comes from the Prospective Urban Rural Epidemiology (PURE) multination-cohort study of 135,335 individuals aged 35-70 years without cardiovascular disease from 18 low-, middle-, and high-income countries (7 geographical regions: North America/Europe, South America, Middle East, south Asia, China, southeast Asia, and Africa). In this study there was less overall mortality and cardiovascular events associated with higher fat intake (including saturate fats) and higher dairy intake (more than 2 servings daily, including butter and cheese). *Note: some have questioned the validity of the PURE study because of methodologic problems, especially confounding by different degrees of socio-economical development in different countries and questionable dietary intake data (Harvard School of Public Health, Nutrition News: https://www.hsph.harvard.edu/nutritionsource/2017/09/08/pure-study-makes-headlines-but-the-conclusions-are-misleading/)*

4. Intervention studies that randomly assign subjects with a disease or medical condition to a plant-based diet vs. a control diet (usually with meat and animal products) have found the following:
   - ✓ Obese or overweight individuals randomized to a vegan or vegetarian diet for up to 1 year lost more weight, reduced BMI, and lowered cholesterol more than those on a vegetarian or omnivorous diet
   - ✓ Obese or overweight individuals, who also had high lipids or cholesterol, randomized to a vegetarian diet (including some eggs and diary) for up to 6 months had lower BMI, triglycerides, LDL cholesterol, total cholesterol, total cholesterol to HDL ratio, and apolipoprotein B to A1 ratio than those on a meat-based diet
   - ✓ Patients with type 2 diabetes randomized to a vegan diet for up to 6 months had better glycemic control, less need for diabetes medications, and lower metabolic factors (hemoglobin A1c, total cholesterol, and LDL cholesterol) than those on a control diet (American Diabetes Association)
   - ✓ Patients with coronary artery disease randomized to a vegetarian diet (including egg whites and low-fat milk) plus lifestyle changes (stress management, moderate exercise, smoking reduction group psychosocial support) for up to 4 years had less coronary artery disease (by angiography) and fewer cardiac events than those on a meat-based diet without any lifestyle intervention
   - ✓ Patients with high cholesterol randomized to a plant-based diet (low fat, added cheese and eggs) for 4 weeks had lower LDL cholesterol than those who ate a low-fate diet with animal products

5. Studies that observed a group of patients with a disease or medical condition who were placed on a plant-based diets have found the following:
   - ✓ Patients with coronary artery disease who voluntarily adopted a low-fat, plant-based diet (including skim milk, yogurt) for up to 12 years reversed, or improved, their coronary disease (angiography)
   - ✓ Patients with fibromyalgia who ate a vegan diet for 3 months had less pain, joint stiffness, and overall rheumatology symptoms than those on a regular diet; vegans also had better sleep and general health
   - ✓ Patients with rheumatoid arthritis who ate a low-fat vegan diet for 4 weeks reduced all arthritis symptoms, except morning stiffness

6. There increasing evidence that individuals who eat whole food, plant-based diets have better health outcomes than individuals who eat refined carbohydrates, some animal products, or both:
   - ✓ Individuals who eat exclusively plant-based diets in population-based and comparative studies have lower rates of obesity, hypertension, type 2 diabetes, and cardiovascular disease than those who eat plant-based diets with some animal products
   - ✓ Individuals who eat high levels of complex carbohydrates (rich in fiber and whole grains) in observational studies have a 15-30% decrease in all-cause and cardiovascular related mortality, and incidence of coronary heart disease, stroke incidence and mortality, type 2 diabetes, and colorectal cancer, compared with individuals who eat high levels of refined carbohydrates

- ✓ Individuals who eat high levels of fiber and/or whole grains in clinical trials have lower body weight, systolic blood pressure, and total cholesterol, compared to individuals who eat low levels of fiber and/or whole grains

Study Types

The purpose of this document is to summarize the best published evidence regarding the impact of plant-based diets on wellness and physical health. This is not an exhaustive list, but instead focuses on English-language articles in human subjects that fall into 4 main categories:

1. Systematic Reviews and High-quality Reviews: Systematic reviews, including meta-analyses, use explicit criteria to reduce bias in locating, appraising, and synthesizing information from multiple research studies to reach valid conclusions. High-quality reviews identify articles with a well-defined literature search and with explicit criteria for including or excluding studies, but may lack the rigorous protocol of a formal systematic review. Reviews are extremely useful in drawing conclusions from a large body of related research, but they are limited by the quality and consistency of the included studies.
2. Randomized Controlled Trials (RCTs): RCTs are experimental studies that provide the highest level of clinical evidence regarding a specific research question. Study participants typically have a baseline condition or disorder (e.g., obesity, diabetes, high cholesterol) and are randomly assigned by the investigators to a plant-based diet or something different (e.g., omnivorous [all foods, including meat] diet, their normal baseline diet, or some other dietary restriction) and then assessed at some future time point for changes from baseline or other measures of health and disease status. RCTs provide the most reliable results because they reduce bias in how people are allocated to different treatment (diet) groups, but the results may not apply outside the study because of intensive intervention in a restricted and narrow subject group that could be difficult to replicate in more pragmatic, real-world settings.
3. Large Cohort Studies: These are performed in large populations of people (healthy and sick) who are surveyed regarding dietary and food habits, and then assessed at the same time, in the future, or both, for various health outcomes. The investigators then look for associations (correlations) between diet and baseline health of future disease states. By using large populations the results can often be broadly applied (generalized), but cohort studies can only discover associations (e.g., relationships) and cannot prove cause and effect.
4. Intervention Studies: Intervention studies begin with one or more groups of people with a specific disease, condition, or disorder and then ask them to follow a specific diet, with or without other lifestyle changes. The study may have one intervention or many, but unlike the RCT there is no random allocation to different groups. Intervention studies are great for showing changes over time (e.g., improvement from baseline), but they are limited by loss of subjects (attrition), limited ability to monitor compliance with the intervention, and by bias in how subjects are selected (often volunteers) or assigned to different interventions (if more than one).

Systematic and High-Quality Review Articles (alphabetical by first author)

1. Aleksandrova K, Koelman L, Rodrigues CE. Dietary patterns and biomarkers of oxidative stress and inflammation: a systematic review of observational and intervention studies. Redox Biol 2021; doi: 10.1016/j.redox.2021.101869. *Systematic review of 16 observational and 13 intervention studies showing that plant-forward diets (Mediterranean, DASH, vegetarian, USDA Health Eating Index) correlated with reduce oxidative stress and proinflammatory biomarkers, whereas an opposite relationship was seen for Western and fast-food diets. Most studies were of low to moderate quality; no data pooling, just individual study results.*
2. Bakaloudi DR, Halloran A, Rippin HL, et al. Intake and adequacy of the vegan diet. A systematic review of the evidence. Clin Nutr 2021; 40:3503-21. *Systematic review of 48 studies (12 cohort, 36 cross-sectional) of European populations with vegan diets comparing macro- and micro-nutrient intakes to WHO recommendations; most studies of good to very good quality. Total protein intake (13-15%) was lower than WHO recommendation (15%), and*

vegans has significantly lower intake of vitamins B2, Niacin (B3), B12, D, iodine, zinc, calcium, potassium, and selenium. No significant differences in fat intake were observed.; no deficiencies in vitamins A, B1, B6, C, E, iron, phosphorus, magnesium, copper, and folate. Vegan diets had a low glycemic load.

3. Benatar JR, Stewart RAH. Cardiometabolic risk factors in vegans: a meta-analysis of observational studies. PLoS One 2018; 13(12):e0209086. doi: 10.1371/journal.pone.0209086. *Systematic review of 40 observational studies, with 12,619 vegans and 179,630 omnivores, that reported 1 or more cardio-metabolic risk factors. Based on food frequency questionnaires in 28 studies, vegans had lower BMI (-1.72 kg/m2, 95% CI -2.30 to -1.16), waist circumference (-2.35 cm, 95% CI -3.93 to -0.76), LDL cholesterol (-0.49 mmol/L, 95% CI, -0.62 to -0.36), triglycerides (-0.14 mmol/L, 95% CI -0.24 to -0.05), fasting blood glucose (-0.23 mmol/L, -0.35 to -0.10), and systolic (-2.56 mm Hg, 95% CI, -4.66 to -0.45) and diastolic pressure (-1.33 mm HG, 95% CI, -2.67 to -0.02). Exception was a subgroup of studies from Taiwan where vegan diets were not associated with more favorable outcomes.*

4. Craddock JC, Neale EP, Peoples GE, Probst YC. Vegetarian-based dietary patterns and their relation with inflammatory and immune biomarkers: a systematic review and meta-analysis. Adv Nutr 2019; doi 10.1093/advances/nmy103. *Systematic review of 30 observational and 10 interventional studies of vegetarian vs. non-vegetarian dietary patterns. Vegetarian-based dietary patterns had lower C-reactive protein (P<.001), fibrinogen (P=.02), ant total leukocyte (P=.02).*

5. Dinu M, Abbate R, Gensini GF, Casina A, Sofi F. Vegetarian, vegan diets and multiple health outcomes: a systematic review with meta-analysis of observational studies. Crit Rev Food Sci Nutr 2017; 22:3640-9. *Systematic review of 86 cross-sectional and 10 cohort studies. Cross-sectional studies showed significantly reduced levels of BMI, total cholesterol, LDL cholesterol and glucose levels in vegans & vegetarians vs. omnivores; cohort studies showed less ischemic heart disease (*RR *0.75, 95% CI 0.68 to 0.82) and less total cancer (*RR *0.92, 95% CI, 0.87 to 0.98), but no differences in total cardiovascular disease, cerebrovascular disease, or mortality (all-cause or cancer-related). Vegans had reduced risk of cancer (*RR *0.85, 95% CI 0.75 to 0.95).*

6. Eichelmann F, Schwingshackl L, Fedirko V, Aleksandrova K. Effect of plant-based diets on obesity-related inflammatory profiles: a systematic review and meta-analysis of intervention trials. Obes Rev 2016; 17:1067-79. *Systematic review of 29 intervention trials showed that plant-based diets had mean reductions of CRP by -0.55 mg/l (95% CI -0.78 to -0.32), IL-6 by -0.25ng/l (05% CI, -0.56 to 0.06), and sICAM -25.07 (95% CI -52.32 to 2.17). Pooled analyses had high heterogeneity but suggest that improved inflammatory profiles could help treat and prevent chronic disease risk.*

7. Field R, Physio M, Pourkazemi F, Turton J, Rooney K. Dietary interventions are beneficial for patients with chronic pain: a systematic review with meta-analysis. *Systematic review of 43 studies of adults with chronic (>3 months) non-cancer musculoskeletal pain (rheumatoid arthritis, fibromyalgia, osteoarthritis, neuropathic pain) with dietary intervention at least 2 weeks (vegetarian/vegan, single-food changes, elimination protocols, energy and/or macronutrient restriction, Mediterranean diet). Overall positive effect found for whole food, plant-based diets on pain (most often with visual analog scale), with no single diet superior. Effect sizes mostly small to moderate (SMD), but some large.*

8. GBD 2017 Diet Collaborators. Health effects of dietary risks in 195 countries, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2019; 393:1958-72. *Systematic review of nationally or subnationally representative nutrition surveys in adults 25 years or older from 195 countries (data collected 1980-2016) and reanalyzed form 1990-2017 for impact of dietary components on morbidity, mortality, and disability-adjusted life years (DALY's). Dietary factors accounted for 11 million deaths in 2017 (22% of all deaths) from non-communicable diseases and 25 million DALY's (15% of total). Leading dietary risk factors for deaths globally were high intake of sodium (3 million), low intake of whole grains (3 million), and low intake of fruits (2 million).*

9. Gibbs J, Gaskin E, Ji C, Miller MA, Cappuccio FP. The effect of plant-based dietary patterns on blood pressure: a systematic review and meta-analysis of controlled intervention trials. J Hypertens 2021; 39:23-37. *Systematic review of 41 clinical trials with adults comparing plant-based diets (vegan, vegetarian, healthy Nordic, Mediterranean, high-fiber, and high-fruit/vegetables) vs. referent or control diet, found that plant-based diets were associated with lower systolic BP (maximum mean reduction 5.5 mmHg) and diastolic BP. No relation to gender or BMI.*

10. Guasch-Ferré M, Satija A, Blondin SA, et al. Meta-analysis of randomized controlled trials of red meat consumption in comparison with various comparison diets on cardiovascular risk factors. Circulation 2019; 139:1828-45. *Systematic review of 36 clinical trials with 1,803 participants randomized to diets with red meat vs. diets that replaced red meat with other foods (e.g., high quality plant protein, chicken/poultry/fish, dairy, low quality carbohydrates). Substituting red meat with high-quality plant protein sources (legumes, soy, nuts), but not with fish or low-quality carbohydrates, lowered total cholesterol, triglyceride, and LDL levels.*

11. Guo J, Astrup A, Lovegrove JA, et al. Milk and dairy consumption and risk of cardiovascular diseases and all-cause mortality: dose-response meta-analysis of prospective cohort studies. Eur J Epidemiol 2017; 32:269-87. *Systematic review of 29 cohort studies (938,465 participant) with 93,158 mortalities, 28,419 coronary heart disease (CHD) cases, and 25,416 cardiovascular disease (CVD) cases. No associations were found for total (high-fat/low-fat) dairy and milk for any health outcomes.*

12. Huang RY, Huang CC, Hu FB, Chavarro JE. Vegetarian diets and weight reduction: a meta-analysis of randomized controlled trials. J Gen Intern Med 2016; 31:109-16. *Systematic review of 12 randomized trials of 1,151 adults (mostly overweight or with type 2 diabetes) comparing vegan or lacto-ovo-vegetarian diets to non-vegetarian diets over a median duration of 4.5 months. The vegetarian group had 2.02 kg greater weight loss (95% CI, 1.23 to 2.80), with greater weight loss for the vegan diet (2.52 kg) than the lacto-ovo-vegetarian diet (1.48 kg), and greater weight loss for subjects followed less than 1 year (2.05 kg) than those followed 1 year or longer (1.13 kg).*

13. Iguacel I, Miguel-Berges ML, Gómez-Bruton A, Moreno LA, Julián C. Veganism, vegetarianism, bone mineral density, and fracture risk: a systematic review and meta-analysis. Nutr Rev. 2019; 77:1-18. *Systematic review of 20 studies (37,134 participants) assessing bone mineral density (BMD) and fracture risk with a vegan, vegetarian, or omnivorous diet. Vegans and vegetarians had lower BMD at the femoral neck and lumbar spine, and vegans also had higher fracture rates (relative risk 1.44, 95% CI, 1.05 to 1.98). Nearly all studies had exclusively women participants, so results cannot be applied to men. Potential variables that were not controlled for in the analyses, but are also associated with BMT and fracture risk, include daily hours of physical activity, duration of vegan/vegetarian diet, BMT, use of hormone replacement therapy, consumption of alcohol, and smoking behavior. Bottom line is that although not definitive, results women who are vegans should be aware of bone health and avoid dietary deficiencies.*

14. Johannesen CO, Dale HF, Jensen C, Lied GA. Effects of plant-based diets on outcomes related to glucose metabolism: a systematic review. Diabetes Metab Syndr Obes 2020; 13:2811-22. *Systematic review of 9 RCTs comparing plant-based dietary intervention vs. omnivorous diet in adults with type 2 diabetes, cardiovascular disease, or obesity/overweight. Most studies (56%) showed plant-based interventions improved glycemic control from baseline to endpoint and some (44%) showed greater improvement in glycemic control for intervention vs. control group; 4 studies showed no differences. Substantial heterogeneity precludes any conclusion about impact of any specific plant-based diet.*

15. Kaiser J, van Daalen KR, Thayyil A, et al. A systematic review of the association between vegan diets and risk of cardiovascular disease. J Nutr 2021; 151:1539-52. *Systematic review of 7 studies (5 prospective cohort, 1 cross-sectional, 1 RCT) with >73,00 adults with about 7,700 vegans assessing association between vegan diets and cardiovascular outcomes. Compared to the least-restrictive other diet in the study (e.g., omnivorous), there was no significant impact of vegan diet on incident, recurrent, or intermediate cardiovascular disease. There was some evidence that vegan diet may prevent recurrent events, but studies were of poor quality. Generalizability limited by varying definitions of vegan diets, some of which allowed refined grains, oils, and starchy vegetables.*

16. Lee J, Fu Z, Chung M, Jang DJ, Lee HJ. Role of milk and dairy intake in cognitive function in older adults: a systematic review and meta-analysis. Nutr J 2018; 27: 17(1):82. doi: 10.1186/s12937-018-0387-1. *Systematic review of 1 small randomized trial and 7 cohort studies concluding that the existing evidence is too poor (high risk of bias, methodological problems) to draw a firm conclusion about the effect of milk or dairy intake on the risk of cognitive decline or disorders in adults.*

17. Lu W, Chen H, Nu Y, et al. Dairy products intake and cancer mortality risk: a meta-analysis of 11 population-based cohort studies. Nutr J 2016; 15:91. DOI 10.1186/s12937-016-0210-9. *Systematic review of 11 cohort studies (778, 929 participants) showing that total dairy products intake is not associated with all-cancer mortality risk (relative risk 0.99, 95% CI, 0.92 to 1.07), with a similar lack of association noted for subgroups (milk, yogurt,*

cheese, and butter in males and females). The only significant relationship was an increased risk of prostate cancer mortality (relative risk 1.50, 95% CI 1.03 to 2.17) in men for whole milk, with dose-response analysis showing a linear relationship and increased risk with a single additional serving per day (relative risk 1.43, 95% CI, 1.13 to 1.81)

18. Menzel J, Jabakhanji A, Biemann R, et al. Systematic review and meta-analysis of the associations of vegan and vegetarian diets with inflammatory biomarkers. Sci Rep 2020;10:21736. doi: 10.1038/s41598-020-78426-8. *Systematic review of 21 cross-sectional studies showing reduced CRP with vegan and vegetarian diets, especially in patients with renal disease, but not for any other inflammatory biomarkers.*

19. Nadal-Ncolás Y, Miralles-Amorós L, MartínezOlcina M, et al. Vegetarian and vegan diet in fibromyalgia: a systematic review. Int J Environ Res Pub Health 2021; 18:4955, doi.org/10.3390/ijerph18094955. *Systematic review of 4 clinical trials and 2 cohort studies (interventions last 3 weeks to 3 months) assessing effect of a vegan or vegetarian diet on fibromyalgia patients. Results showed significant improvements in biochemical parameters, quality of life, quality of sleep, pain at rest, and general health status following mainly plant-based dietary patterns, but confidence limited by risk of bias and heterogeneity.*

20. Pollakova D, Andreadi A, Pacifici F, et al. The impact of vegan diet in the prevention and treatment of type 2 diabetes: a systematic review. Nutrients 2021; 13:2123, doi.org/10.3390/nu13062123. *Systematic review of 7 observational and 8 RCTs (fair to good quality) assessing vegan diets and type 2 diabetes (T2D) glycemic control and diabetes-related complications. Data not suitable for pooling, but vegan diet was associated with lower T2D prevalence, lower T2D incidence, and improved glucose levels and glycemic control. Most showed better BMI, cholesterol, blood pressure with vegan diet, and 1 study showed reduced foot pain.*

21. Rinaldi S, Campbell EE, Fournier J, O'Connor C, Madill J. A comprehensive review of the literature supporting recommendations from the Canadian Diabetes Association for the use of plant-based diet for management of type 2 diabetes. Can Diabetes 2016; 40:471-7. *Systematic review of 13 intervention and large observations studies of plant-based diets as medical nutrition therapy. Studies reported that plant-based diets improved A1C levels, BMI, body weight, waist circumference, quality of life scores, and fasting blood glucose; decreases total cholesterol, LDL cholesterol, non-HDL cholesterol, and depressions; and resulted in oral hypoglycemic medication discontinuation.*

22. Kwok CS, Umar Saadia, Myint PK, Mamas, MA, Loke YK. Vegetarian diet, Seventh Day Adventists and risk of cardiovascular mortality: a systematic review and meta-analysis. Int J Cardiol 2014; 176:680-6. *Meta-analysis of 8 observational studies (183,321 participants) comparing a vegetarian/non-meat group with a control group (either general population or meat-eaters) that aimed to evaluate cardiovascular mortality. Risk of bias was moderate for 5 studies and low for 2, with all studies assessing dietary intake with questionnaires. For all outcomes, studies in Seventh Day Adventists (SDA) cohorts had greater effect sizes compared with non-SDA cohorts for reduced overall mortality (SDA -32%, 95% CI, -55 to 2% vs. non-SDA +4%, 95% CI, -2 to 10%), mortality from ischemic heart disease or a cardiac event (SDA -40%, 95% CI -57 to -17% vs. non-SDA -16%, 95% CI -26 to -4%), and cerebrovascular disease mortality (SDA -29%, 95% CI -59 to 20% vs. non-SDA +5%, 95% CI -11 to 24%). All analyses had high heterogeneity. Conclude that vegetarian diet has modest cardiovascular benefit, but no clear reduction in overall mortality; evidence in driven mainly by SDA results and effect of vegetarian diet in other cohorts is unproven.*

23. Le LT, Sabate J. Beyond meatless, the health effects of vegan diets: findings from the Adventists Cohorts. Nutrients 2014; 6:2131-47. *Systematic review of 13 articles based on 3 prospective cohorts – Adventist Mortality Study, Adventist Health Study, and Adventist Health Study-2 – reporting clearly defined dietary patterns as exposures and comparing vegetarians (about 50% [8% vegans]) to non-vegetarians (50%) for cardiometabolic factors, cancer-related sites, and/or mortality. Compared to omnivorous diets, vegetarians (including vegans) had reduced odds of hypertension (55%), diabetes (49%), metabolic syndrome* (56%), colon cancer (45-51%), GI cancer (23%), all-cause mortality (12-20%), and cardiovascular mortality for men only (29%); overall cancer rates reduced by 7-8% but not statistically significant (95% CI, -3 to 19%). A subgroup analysis comparing lacto-ovo-vegetarians to vegans showed that vegan diets offer additional protection for obesity, hypertension, type-2 diabetes, and cardiovascular mortality; in one study, vegans had 73% higher odds of urinary tract cancer. [*metabolic syndrome defined as having at least 3 of the following 5 conditions: abdominal obesity, high blood pressure, high blood sugar, high serum triglycerides, and low HDL levels]*

24. Lopez PD, Cativo EH, Atlas SA, Rosendorff C. The effect of vegan diets on blood pressure in adults: a meta-analysis of randomized controlled trials. Am J Med 2019; doi.org/10/1016/j.amjmed.2019/01.044. *Systematic review of 11 randomized, controlled trials with 983 participants, showing that a vegan diet, compared to "any less restrictive diet," di not reduce systolic or diastolic blood pressure; subgroup analysis of studies with baseline hypertension (systolic BP ≥ 130 mm Hg) showed small decreases in systolic BP (- 4.10 mm Hg, P=0.047) and diastolic BP (-4.01 mm Hg, P<.001).*

25. Lowry E, Marley J, McVeigh JG, McSorley E, Allsopp P, Kerr D. Dietary interventions in the management of fibromyalgia: a systematic review and best-evidence synthesis. Nutrients 2020; 12: 2664. doi: 10.3390/nu12092664. *Systematic review of 18 RCTs and 4 cohort studies, with 806 adults, of 17 different nutritional interventions, with significant improvement in pain in one vegan study; conclude insufficient evidence to recommend any specific dietary approach.*

26. Namazi N, Saneei P, Larijani B, Esmaillzadeh A. Soy product consumption and the risk of all-cause cause, cardiovascular, and cancer mortality: a systematic review and meta-analysis of cohort studies. Food Funct 2018; 23:2576-88. *Systematic review of 7 studies with 627,209 participants and 39,250 deaths in 7 to 18 years of follow-up. No significant associations were found between a high intake of soy products and all-cause, cardiovascular, and cancer mortality.*

27. Papimichou D, Panagiotakos DB, Itsiopoulos C. Dietary patterns and management of type 2 diabetes: a systematic review of randomized trials. Nutr Metabol Cardiovasc Dis 2019; doi.org/10/1016/numecd.2019.02.004. *Systematic review of 15 intervention trials of duration 6 months or longer comparing dietary patterns and management of type 2 diabetes. Mediterranean dietary pattern showed greatest reduction in body weight, HbA1c levels, and delayed requirement for diabetes medications; vegan and macrobiotic diet showed improved glycemic control; vegetarian diet showed greater body weight reduction and insulin sensitivity. No quantitative analysis or data pooling.*

28. Poulsen NB, Lambert MNT, Jeppesen PB. The effect of plant derived bioactive compounds on inflammation: a systematic review and meta-analysis. Mol Nutr Food Res 2020; 64: e2000473. doi: 10.1002/mnfr.202000473. *Systematic review of 16 RCTs (12 parallel group, 4 crossover) with 1,161 participants who were healthy or had comorbidities (e.g., overweight, diabetes, metabolic syndrome, high cholesterol). Plant-based diets and products (oils, such as flaxseed, grapeseed, rapeseed, corn, olive, safflower) significantly reduced C-reactive protein overall, and in diabetic, obese, and overweight patients. Small to moderate effect sizes with high heterogeneity.*

29. Qian F, Liu G, Hu FB, et al. Association between plant-based dietary patterns and risk of type 2 diabetes: a systematic review and meta-analysis. JAMA Intern Med 2019; : 10.1001/jamainternmed.2019.2195 . *Systematic review of 9 prospective cohorts with 307,099 adults, and 23,544 cases of incident type 2 diabetes. Higher adherence to a plant-based dietary pattern reduce diabetes risk by 23% (RR 0.77, 95% CI, 0.71 to 0.84) compared with poorer dietary adherence; subset analysis of 5 studies using plant-based dietary indices showed a linear, dose-response relationship between more plant-based foods and lower risk of diabetes.*

30. Reynolds A, Mann J, Cummings J, et al. Carbohydrate quality and human health: a series of systematic reviews and meta-analyses. Lancet 2019; 393:434-45. *Systematic review of 185 prospective studies (135 million person-years of data) and 58 clinical trials (4,635 adult participants) comparing the highest vs. lowest consumption of whole grains and carbohydrates rich in fiber. Observational studies showed a 15-30% decrease for the highest consumers in all-cause and cardiovascular related mortality, and incidence of coronary heart disease, stroke incidence and mortality, type 2 diabetes, and colorectal cancer. Clinical trials showed that the highest consumers had significantly lower body weight , systolic blood pressure, and total cholesterol. Consuming 25-29 grams of fiber daily conferred greatest risk reduction and dose-response curves showed that higher consumption could protect against cardiovascular disease, type 2 diabetes, colorectal and breast cancer. Certainty of evidence was moderate for fiber outcomes and low to moderate for whole grains.*

31. Schwingshackl L, Schwedhelm C, Hoffmann G, et al. Food groups and risk of all-cause mortality: a systematic review and meta-analysis of prospective studies. Am J Clin Nutr 2017; 105:1462-73. *Systematic review of 102 studies of association between 12 nutrient groups and all-cause mortality (studies: whole grains 19, refined grains 4, vegetables 37, fruits 34, nuts 16, legumes 17, egg consumption 8, dairy products 25, fish 37, red meat 10,*

processed meat 7, and sugar-sweetened beverages (SSB) 5). The risk of all-cause mortality decreased with increasing intake (for each daily serving of whole grains (RR 0.92), vegetables (RR 0.96), fruits (RR 0.94), nuts (RR 0.76), and fish (RR 0.93). Conversely, mortality increased with higher intake of red meat (RR 1.10) and processed meat (RR 1.23). Dairy products increased mortality in a non-linear fashion, with no detrimental effects for intake up to 750 g/d but a 15% increased risk of mortality above this level. Refined grains and SSBs did not show significant relations.

32. Segovia-Siapco G, Sabaté J. Health and sustainability outcomes of vegetarian dietary patterns: a revisit of the EPIC-Oxford and the Adventist Health Study-2 cohorts. Eur J Clin Nutr. 2018 Oct 2. doi: 10.1038/s41430-018-0310-z. *Narrative review comparing 2 ongoing, longitudinal studies with large proportions of vegetarians (essentially no meat intake, but some fish), with new emphasis on sustainability. Risk for all cancers was 16% lower in AHS-2 study for vegans and 11-19% lower in EPIC-Oxford for vegetarians and fish-eaters; morbidity and chronic diseases were overall lower in vegetarians. Greenhouse gas emissions of equicaloric diets were 29% less in vegetarian diet in AHS-2 and 47-60% less for vegetarian/vegan diets in EPIC-Oxford than non-vegetarian/meat-eating diets. Conclude that the beneficial health outcomes and reduced carbon footprints make the case for adoptiing vegetarian diets to address global food supply and environmental sustainability.*

33. Soedamah-Muthu SS, de Goede J. Dairy consumption and cardiometabolic diseases: systematic review and updated meta-analyses of prospective cohort studies. Current Nutrition Reports 2018; 7:171-82. *Update of a 2011 meta-analysis (17 studies) with 9 newer studies. Total dairy and low-fat dairy reduced the risk of diabetes by 3 to 4%, with a larger impact for yogurt (relative risk 0.86, 95% CI 0.83 to 0.90). Total dairy and milk were not associated with coronary heart disease.*

34. Toumpanakis A, Turnbull T, Alba-Barba I. Effectiveness of plant-based diets in promoting well-being in the management of type 2 diabetes: a systematic review. BMJ Open Diabetes Res Care. 2018 Oct 30;6(1):e000534. doi: 10.1136/bmjdrc-2018-000534. *Systematic review of 9 unique controlled (7 randomized) trials (433 participants, mean age 55 years) of plant-based diet interventions for adults with type 2 diabetes. Plant-based diets were associated with significant improvement in emotional well-being, physical well-being, depression, quality of life, general health, HbA1c levels, weight, total cholesterol and low-density lipoprotein cholesterol, compared with several diabetic associations' official guidelines and other comparator diets. No forest plots or data pooling.*

35. Tran E, Dale HF, Jensen C, Lied GA. Effects of plant-based diets on weight status: a systematic review. Diabetes Metab Syndr Obes 2020; 13:3433-48. *Systematic review of 19 studies, mostly RCTs, comparing low-fat vegan diet to an omnivore diet in overweight adults with type 2 diabetes and/or cardiovascular disease, for which 8 studies showed significant reduction in body weight and/or BMI for plant-based group; no data pooling.*

36. Valli C, Rabassa M, Johnston BC, et al. Health-related values and preferences regarding meat consumption: a mixed-methods systematic review. Ann Int Med 2019. Doi:10.7326M/19-1326. *Qualitative review of 41 quantitative and 13 qualitative studies that concluded, based on low-certainty evidence with limited generalizability, that omnivores (a) consider meat an essential component of a healthy diet (18 studies), (b) enjoy eating meat (13 studies), (c) have low willingness to reduce their meat consumption (9 studies), and (d) lack the skills needed to prepare satisfactory meals without meat (7 studies). Vegetarians and low meat consumers reported health as 1 of the main reasons for not eating meat (23 studies).*

37. Yokoyama Y, Levin SM, Barnard ND. Association between plant-based diets and plasma lipids: a systematic review and meta-analysis. Nutr Rev 2017; 75:683-98. *Systematic review of 30 observational studies and 19 clinical trials assessing association of plant-based diets (for at least 4 weeks) and plasma lipids. Compared to omnivorous diets, participants on vegetarian diets showed greater reductions from baseline in cholesterol (-29.2 vs. -12.5 mg/dL, P<.001) and LDL cholesterol (-22.9 vs. -12.2, P<.001), but no differences in triglycerides.*

38. Yokoyama Y1, Nishimura K2, Barnard ND3, et al. Vegetarian diets and blood pressure: a meta-analysis. JAMA Intern Med. 2014; 174:577-87. *Systematic review of 7 clinical trials (311 adults) and 32 observational studies (21,604 adults) assessing the change in blood pressure (BP) after vegetarian diet as an exposure or intervention. In the clinical trials, vegetarian diets reduced mean systolic BP by 4.8 mm Hg (95% CI, 3.1 to 6.6) and diastolic BP by 2.2 mm Hg (95% CI, 1.0 to 3.5). In the observational studies, the mean systolic BP reduction was 6.9 mm Hg (95% CI, 4.7 to 9.1) and the diastolic reduction was 4.7 mm Hg (95% CI, 3.1 to 6.3).*

39. Wang F, Zheng J, Yang B, et al. Effects of vegetarian diets on blood lipids: a systematic review and meta-analysis of randomized controlled trials. J Am Heart Assoc 2015; 4: 10):e002408. doi: 10.1161/JAHA.115.002408. *Systematic review of 11 clinical trials with 832 participants that randomized participants to a vegetarian vs. omnivore diet and assessed blood lipids. Vegetarian diets lowered blood concentrations of total cholesterol by 0.36 mmol/L (95% CI, 0.17 to 0.55), LDL cholesterol by 0.34 mmol/L (95% CI, 0.11 to 0.57), and HDL cholesterol by 0.30 (95% CI, 0.10 to 0.50). There was no impact of diet on blood triglyceride levels.*

40. Wu J, Zeng R, Huang J, et al. Dietary protein sources and incidence of breast cancer: a dose-response meta-analysis of prospective studies. Nutrients 2016; 8,730; doi:10.3390/nu8110730. *Systematic review of 46 prospective studies. High soy consumption reduced the risk of breast cancer by 8% relative to low soy consumption in 10 studies with 452,916 participants (relative risk 0.92, 95% CI 0.84 to 1.00). A linear association was observed between soy food intake and decreased breast cancer risk. In contrast, total red meat intake increased breast cancer risk by 7% in 8 studies with 691,383 participants (relative risk 1.07, 95% CI 1.01 to 1.07). No associations were found for poultry, fish, egg, nuts, total milk, and whole milk intake.*

Randomized Controlled Trials of Plant-based Diets vs. Alternatives

Overweight or obese samples

1. Barnard ND, Scialli AR, Turner-McGrievy G, et al. The effects of a low-fat, plant-based dietary intervention on body weight, metabolism, and insulin sensitivity. Am J Med 2005; 118:991-7. *64* ***overweight****, post-menopausal women randomized to low-fat vegan diet vs. control diet (Nat'l Cholesterol Education Program) without limits on portion size or energy intakeD for 14 weeks. Vegan group had higher weight loss (P=.012) and increased insulin sensitivity (P=.017) vs. control group.*

2. Hall KD, Guo J, Courville AB, et al. Effect of plant-based, low-fat diet versus and animal-based, ketogenic diet on ad libitum energy intake. Nat Med 2021; 27:344-53. *(NB: "ad libitum" mean "as much or as often as necessary or desired"). 20 adults, mean age 30y with BMI 28, randomized to consume ad libitum a minimally processed, plant-based low-fat diet (10% fat, 75% carbohydrate) with high glycemic load vs. minimally processed, animal-based ketogenic, low-carbohydrate diet (76% fat, 10% carbohydrate with low glycemic load for 2 weeks, then cross-over for additional 2 weeks. Low-fat diet let to 689 kcal/day less energy intake than the low-carbohydrate diet over 2 weeks (which was the opposite of traditional teaching, that high carbohydrate diets lead to excess insulin secretion, promoting fat accumulation and increased energy intake).*

3. Kahleova H, Dort S, Holubkov R, Barnard ND. A plant-based high-carbohydrate, low-fat diet in overweight individuals in a 16-week randomized controlled trial: the role of carbohydrates. Nutrients 2018; 10:doi: 10.3390/nu10091302. *75* ***overweight*** *adults without diabetes randomized to a plant-based high-carbohydrate, low-fat (vegan) diet vs. their current diet. Vegan diet had 6.5 kg more weight loss (95% CI, 4.1 to 8.9), 4.3 kg more fat reduction (95% CI, 3.2 to 5.4), and significantly reduced insulin resistance. Increased carbohydrate intake (as a percentage of energy) correlated significantly (P<.001) with reduced body mass index (r 0.53), fat mass (r 0.55), visceral fat (0.35), and insulin resistance (0.27). Similar associations were observed for increased consumption of total and insoluble fiber. A sub-analysis in a spin-off study (Nutr Diabetes. 2018 Nov 2;8(1):58. doi: 10.1038/s41387-018-0067-4) found that the decrease in fat mass was associated with an increased intake of plant protein (r -0.30, P-0.011) and decreased intake of animal protein (r +0.39, P=.001).*

4. Kahleova H, Petersen KF, Shulman GI, et al. Effect of a low-fat vegan diet on body weight, insulin sensitivity, postprandial metabolism, and intramyocellular and hepatocellular lipid levels in overweight adults. JAMA New Open 2020; 3: doi: 10.1001/jamanetworkopen.2020.25454. *Clinical trial of 244 overweight adults, age 25-75y, randomized to low-fat vegan diet vs. control (no diet changes) for 16 weeks; vegan diet reduced body weight, reduced energy intake, increase postprandial metabolism. Reductions in hepatocellular and intramyocellular fat were associated with increased insulin sensitivity.*

5. Meir AY, Rinott E, Tsaban G, et al. Effect of green-Mediterranean diet on intrahepatic fat: the DIRECT PLUS randomized controlled trial. Gut 2021; Epub ahead of print: doi:10.1136/gutjnl-2020-323106. *Clinical trial of 294 adults (mean age 51y, 88% men) with abdominal obesity/dyslipidemia randomized for 18 months to healthy dietary guidelines (HDG) vs. Mediterranean (MED) vs. green-MED weight-loss diet groups, all accompanied by physical activity (90% retention at 18m, 78% had follow-up scans). Introduce new concept of "green-MED" diet, enriched with specific green polyphenols as Mankai, green tea, and walnuts, and restricted in red and processed meat. Prevalence of non-alcoholic fatty liver disease (NAFLD; defined as >5% fat in absence of alcohol abuse) declined from mean of 60-62% at baseline to 55% in HDG group, 48% for MED, and 31% for green-MED (P=0.012, between groups). Despite modest weight loss (HDG 0.5 kg, MED/green-MED 3-4 kg) the green-MED group had almost double intrahepatic fat (IHF) loss vs. MED group (39% vs. 20%, weight loss adjust) and HDG group had smallest change (-12%).*

6. Sofi F, Dinu M, Paglai G, et al. Low-calorie vegetarian versus Mediterranean diets for reducing body weight and improving cardiovascular risk profile: CARDIVEG stud (Cardiovascular Prevention with Vegetarian Diet). Circulation 2018; 137:1103-1113. *118 overweight omnivores, with a low-to-moderate cardiovascular risk profile randomized to a lacto-ovo-vegetarian diet vs. a low-calorie Mediterranean diet for 3 months with a cross-over design. Both diets had similar reductions in body weight (1.8-1.9 kg), body mass index, and fat mass. The vegetarian diet was more effective in lowering LDL cholesterol but the Mediterranean diet was better for triglycerides.*

7. Turner-McGrievy GM, Barnard ND, Scialli AR. A two-year randomized weight loss trial comparing a vegan diet to a more moderate low-fat diet. Obesity 2007; 15:2276-81. *64* ***overweight*** *postmenopausal women randomized to vegan or National Cholesterol Education Program (NCEP) diet for 14 weeks. Vegan diet had significantly greater weight loss at 1 year (11 vs. 4 lbs) and 2 years (7 vs. 2 lbs), with additional benefits when combined with group support meetings.*

8. Turner-McGrievy GM, Wirth MD, Shivappa N, et al. Randomization to plant-based dietary approaches leads to larger short-term improvements in dietary inflammatory index scores and macronutrient intake compared with diets that contain meat. Nutr Res 2015; 35:97-106. *64* ***overweight and obese*** *adults (BMI 25-50) randomized to dietary instruction on vegan (n=12), vegetarian (13), pescovegetarian (13), semivegetarian (13), or omnivorous (12) diet for 6 months. Vegan diet compared to others showed greater improvements in fiber, carbohydrate, fat, saturated fat, cholesterol, and the Dietary Inflammatory Index scores at 2 and 6 months.*

9. Turner-McGrievy GM, Davidson CR, Wingard EE, Wilcox S, Frongillo EA. Comparative effectiveness of plant-based diets for weight loss: a randomized controlled trial of five different diets. Nutrition 2015; 31:350-8. *Reports a different endpoint (weight loss) on the same patients studied in the 2015 article by the first author in Nutrition Research (64 adults with* ***BMI 25-50****, 12 randomized to vegan diet, 12 omnivorous, and remainders different vegetarian). Vegan diet had greater weight loss than other groups at 6 months (-7.5% vs. -3.2%, P=.03) and had greater decreases in fat and saturated fat (P<.05).*

10. Wright N, Wilson L, Smith M, Duncan B, McHugh P. The BROAD study: a randomized controlled trial using a whole food plant-based diet in the community for obesity, ischaemic heart disease or diabetes. Nutrition & Diabetes 2017; 7: e256; doi:10/1038/nutd.2017.3. *65 adults age 35-70 years who were* ***obese/overweight*** *and had 1 or more chronic disease (type 2 diabetes, ischemic heart disease, hypertension, or hypercholesterolemia) randomized to whole-food plant-based diet (7-15% fat with no energy restrictions) vs. control group with normal care for 12 months. Plant-based group lost about 25 lbs more than control group after 1 year and showed greater improvements in BMI, and cholesterol.*

Cholesterol, lipids, and cardiovascular risk

11. Asnicar F, Berry SE, Valdes AM, et al. Microbiome connections with host metabolism and habitual diet from 1,098 deeply phenotyped individuals. *Secondary analysis of the PREDICT trial (Personalised Responses to Dietary Composition Trial), in which 1,098 health adults, age 18-65y, were randomized to standardized "test" meals vs. captured "free-living" non-standardized meals, to predict and individual's metabolic response to foods based on their microbiome, meal composition, and meal context. Microbial biomarkers for obesity were reproducible and consistent with external cohorts and correlated with circulating blood metabolites that indicate cardiovascular disease. Moreover, the microbiome associated with health dietary habits overlapped those associated with favorable cardiometabolic and postprandial*

markers, suggesting the microbiome could be stratified into generalizable health levels in individuals without clinically manifest disease.

12. Bergeron N, Chiu S, Williams PT, et al. Effects of red meat, white meat, and nonmeat protein sources on atherogenic lipoprotein measures in the context of low compared with high saturated fat: a randomized controlled trial. Am J Clin Nutr 2019; Jun 4. pii: nqz035. doi: 10.1093/ajcn/nqz035. [Epub ahead of print]. *Healthy men and women aged 21-65y, BMI 20-35, randomized 1 of 2 parallel arms (high or low saturated fatty acid [SFA] diet) then allocated to 4 weeks each of red meat, white, meat, an nonmeat protein diets in random order. Nonmeat protein reduces LDL cholesterol and apolipoprotein B (apoB), independent of SFA status; no differences seen for white vs. red meat. High SFA diet increased LDL cholesterol, apoB, and large LDL independent of protein source.*

13. Crimarco A, Springfield S, Petlura C, et al. A randomized crossover trial on the effect of plant-based compared with animal-based meat on tremthylamine-N-oxide (TMAO) and cardiovascular disease risk factors in generally healthy adults: Study With Appetizing Plantfood – Meat Eating Alternative Trial (SWAP-MEAT). Am J Clin Nutr 2020; 112:1188-99. *Study funded by unrestricted grant from Beyond Meat to Stanford University. Crossover trial of 36 adults randomized to 2 or more servings/day of plant vs. animal meat for 8 weeks, keeping other consumption stable. TMAO concentrations were significantly lower overall for plant vs. animal (2.7 vs. 4.7, P=.012), but only for the 18 participants who received plant second (after crossover) and not for those who received plant first; LDL cholesterol concentrations were also lower during the plant meat phase (110 vs. 121 mg/dL, P=.002).*

14. Gardner CD, Coulston A, Chatterjee L, et al. The effect of a plant-based diet on plasma lipids in hypercholesterolemic adults: a randomized trial. Ann Intern Med 2005; 142:725-33. *120 adults (age 30-65y) with **LDL cholesterol of 130-190 mg/dl**, and a BMI <31 with otherwise good health, randomized to a plant-based diet (low fat plus some added cheese and eggs) vs. low-fat diet with animal products (both diets had identical total fat, saturated fat, protein, carbohydrate, and cholesterol content) for 4 weeks; plant-based diet had greater effect in lowering total and LDL cholesterol (P=0.02) but not on HDL or triglycerides.*

15. Jakše B, Jakše B, Pajek J, Pajek M. Effects of *ad libitum* consumed low-fat, high-fiber plant-based diet supplemented with plant-based meal replacements on cardiovascular risk factors. Food Nutr Res 2019; May 21;63. doi: 10.29219/fnr.v63.1560. eCollection 2019. *Single-arm intervention trial of 36 adults on a traditional western-type diet switched to a whole food plant-based diet eaten ad libitum (as much as they wanted), including 2 plant-based meal replacements daily, for 10 weeks. Reductions seen in LDL cholesterol of 06 mmol/L (95% CI, 0.3 to 0.8, with similar decrease in non-HDL and total cholesterol. HDL cholesterol was reduced by 0.16 mmol/L (95% CI, 0.2 to 0.2).*

Overweight (or obese) and high lipids/cholesterol

16. Jenkins DJ, Wong JM, Kendall CW, et al. The effect of a plant-based low-carbohydrate ("Eco-Atkins") diet on body weight and blood lipid concentrations in hyperlipidemic subjects. Arch Intern Med 2009; 169; 1046-54. *47 **overweight hyperlipidemic** adults randomized to a plant-based diet (carbohydrates 26%, vegetable protein 31%, vegetable oil 43%) vs. a lacto-ovo vegetarian diet (carbohydrates 58%, protein 16%, fat 25%) for 4 weeks. Plant-based group had greater reductions in LDL-C (-8.1%, P=.002), total cholesterol to HDL-C ratio (-8.7%, P=.004), and apolipoprotein B/A1 ratios (-9.6%, P=.001). Similar weight loss (about 8.8 lbs) in both groups.*

17. Jenkins DJ, Wong JM, Kendal CW, et al. Effect of a 6-month vegan low-carbohydrate ("Eco-Atkins") diet on cardiovascular risk factors and body weight in hyperlipidemic adults: a randomized controlled trial. BMJ Open 2014; 4:e0003505. doi: 10/1136/bmjopen-2013-003505. *39 **overweight hyperlipidemic** men and postmenopausal women randomized to a plant-based diet (carbohydrates 26%, vegetable protein 31%, vegetable oil 43%) vs. a lacto-ovo vegetarian diet (carbohydrates 58%, protein 16%, fat 25%) for 6 months. 23 completed the study (50% plant-based, 68% control) with similar weight loss (about 22 lbs), but plant-based group had greater reductions in LDL-C (P<.001), triglycerides (P=.005), total cholesterol to HDL-C ratio (P<.001), and apolipoprotein B:A1 ratios (P<.001).*

18. Macknin M, Kong T, Weier A, et al. Plant-based no added fat or American Heart Association Diets' impact on cardiovascular risk in obese hypercholesterolemic children and their parents. J Pediatr 2015;

166:953-9. *30 children-parent pairs with* ***child BMI>95th percentile and child cholesterol >169 mg/dL*** *randomized to a plant-based vs. American Heart Association diet for 4 weeks with weekly 2 hour nutrition education classes. Plant-based group had lower BMI scores, total cholesterol, LDL, and HgB A1C; plant-based group also had higher hsCRP levels.*

Diabetic samples

19. Barnard ND, Jenkins CJ, Turner-McGrievy G, et al. A low-fat vegan diet improves glycemic control and cardiovascular risk factors in a randomized clinical trial in individuals with type 2 diabetes. Diabetes Care 2006; 29:1777-83. *99* ***type 2 diabetics*** *randomized to low-fat vegan diet vs. control diet (American Diabetes Association) for 22 weeks. Both diets improved glycemic control and lipid control, with greater benefits for vegan diet; 43% of vegan group reduced diabetes medications.*

20. Barnard ND, Jenkins CJ, Turner-McGrievy G, et al. A low-fat vegan diet and a conventional diabetes diet in the treatment of type 2 diabetes: a randomized, controlled, 74-wk clinical trial. Am J Clin Nutr 2009; 89:1588S-96S. *99* ***type 2 diabetics*** *randomized to a low-fat vegan diet vs. control diet (American Diabetes Association) for 74 weeks. Both diets had sustained reductions in weight an plasma lipids. When controlling for medication changes, the low-fat vegan diet was better than the control diet in lowering Hb A(1c) (-.40 vs. .01, P=.03), total cholesterol (-20.4 vs. -6.8 mg/dL, P=.01), and LDL cholesterol (-13.5 vs. -3.4 mg/dL, P=.03).*

21. De Natale C, Annuzzi G, Bozzetto L, et al. Effects of a plant-based high-carbohydrate/high-fiber diet versus high-monunsaturated fat/low-carbohydrate diet on postprandial lipids in type 2 diabetic patients. Diabetes Care 2009; 32:2168-73. *Randomized, crossover study of 18* ***type 2 diabetic*** *patients (mean age 59, mean BMI 27) who followed either a plant-based high-carbohydrate & high fiber diet vs. a low-carbohydrate diet high in monounsaturated fats (e.g., red meat, whole milk, nuts, avocados) for 4 weeks, followed by crossover; plant-based diet significantly decreased postprandial plasma glucose, insulin responses, and glycemic variability, with additional positive effects on triglyceride-rich lipoproteins.*

Coronary artery disease samples

22. Ornish D, Brown SE, Scherwitz LW, et al. Can lifestyle changes reverse coronary heart disease? The Lifestyle Heart Trial. Lancet 1990; 336:129-33. *28 adults with* ***coronary artery disease*** *(documented by angiography) randomized to low-fat (10%) vegetarian diet (egg whites and 1 cup of milk/yogurt per day allowed) with lifestyle interventions (stress management training, moderate exercise, smoking reduction, and group psychosocial support) vs. control group with no lifestyle changes for 1 year. Coronary angiography showed reduced stenosis diameter of 5.5% for intervention group vs. 7.4% increase for control group; overall, 82% of intervention group showed regression of coronary artery disease. Intervention group has greater decreases in total cholesterol (P=.019), LDL cholesterol (P=.007), and apolipoprotein B (P=.010) than control group.*

23. Ornish D, Scherwitz LW, Billings, et al. Intensive lifestyle changes for reversal of coronary heart disease. JAMA 1998; 280:2001-7. *4-year extension of 1990 randomized trial in Lancet, now with 48 adults with moderate-severe* ***coronary artery disease*** *(documented by angiography). Primary outcome was stenosis seen on coronary angiography. Compared to the control group, the intervention group had greater reduction in stenosis at 1 year (4.5% improvement vs. 5.4% worsening, statistical significance not stated) and after 5 years (7.9% improvement vs. 27.7% worsening, P<.001). Risk ratio for cardiac events was higher for controls: RR=2.47 (95% I, 1.48 – 4.20).*

24. Shah B, Newman JD, Woolf K, et al. Anti-inflammatory effects of a vegan diet vs. the American Heart Association-recommended diet in coronary artery disease (EVADE CAD) trial. J Am Heart Assoc. 2018 Dec 4;7(23):e011367. doi: 10.1161/JAHA.118.011367. *Randomized, open-label trial with blinded study endpoint of 100 adults (mean age 61 years, 85% male) with angiographically defined* ***CAD*** *(≥50% lestion in an artery with ≥2 mm caliber), without prior myocardial infarction or bypass surgery in prior 3 months, randomized to vegan vs. AHA-recommended diet for 8 weeks. Vegan group had 32% lower (95% CI, 6 to 51%) high-sensitivity C-reactive protein, an inflammatory marker of risk for major adverse cardiovascular outcomes in CAD, and also had 13% reduction in LDL cholesterol (95% CI, 3 to 22%).*

Cancer sample

25. Dewell A, Weidner G, Sumner MD, Chi CS, Ornish D. A very low-fat vegan diet increases intake of protective dietary factors and decreases intake of pathogenic dietary factors. J Am Diet Assoc 2008; 108:347-56. *93 patients with* ***early-stage prostate cancer*** *randomized to very low-fat (10%) vegan diet supplemented with soy protein and lifestyle changes vs. control group of usual care for 1 year. Vegan diet increased protective nutrients and phytochemicals (e.g., fiber from 31 to 59 grams/day) and decreased intake of dietary factors implicated in chronic diseases.*

26. Jacka FN, O'Neil A, Opie R, et al. A randomized controlled trial of dietary improvement for adults with major depression (the 'SMILES' trial). BMC Med 2017; 15:23. DOI 10.1186/s12916-017-0791-y. *Adults with moderate-severe depression (N=67) randomized to adjunctive nutritional counseling (7 sessions with clinical dietician) vs. social support protocol for 12 weeks. Diet emphasized whole grains, vegetables, fruit, legumes, nuts (raw, unsalted), olive oil (3 tbsp/day), eggs, low-fat dairy; some fish, chicken, lean red meat; diet restricted sweets, refined cereals, fried food, fast food, processed meats, sugar-sweetened beverages; allowed some red wine with meals. After 12 weeks, the Montgomery-Asberg Depression Rating Scale showed much larger improvement in diet group (Cohen's d, -1.16), with 80% remission (vs. 32% for controls); number needed to treat for remission of 4.1*

Multiple sclerosis sample

27. Yadav V, Marracci G, Kim E, et al. Low-fat plant-based diet in multiple sclerosis: a randomized controlled trial. Mult Scler Relat Disord 2016; 9:80-90. *61 patients with multiple sclerosis (mean age 42 years) randomized to a very low-fat plant-based diet or a wait-listed (control) group for 1 year. No difference seen in brain MRI outcomes, number of MS relapses, or disability at 12 months, but the plant-based diet group at 6 months showed reduced LDL cholesterol, total cholesterol, and fatigue scores.*

Multi-morbidity samples

28. Klementova M, Thieme L, Haluzik M, et al. A plant-based gastrointestinal hormones and satiety more than an energy- and macronutrient processed-meat meal in T2D, obese, and healthy men: A three-group randomized crossover study. Nutrients 2019; 11(1). pii: E157. doi: 10.3390/nu11010157. *Sixty men, aged 30-65 years, in 3 groups of 20 each (healthy, obese, and type 2 diabetes) were randomized to one of two meals matched for energy and micronutrients, either a processed-meat and cheese burger (M-meal) or a vegan meal with tofu (V-meal). GI hormones and satiety were assessed at 30, 60, 120, and 180 minutes after eating, and on the next day given the other meal with similar measurements. Repeated measures ANOVA showed increased satiety after the V-meal for all 3 groups: a 9% increase (95% CI, 4.4-13.6%) for diabetics, an 18.7% increase (95% CI, 12.8-24.6%) in obese men, and a 24.6% increase (95% CI, 18.2-31.7%) in healthy men. Gut hormones were also significantly higher after the V-meal in all groups.*

29. Mishra S, Xu J, Agarwal U, Gonzales J, Levin S, Barnard ND. A multicenter randomized controlled trial of plant-based nutrition program to reduce body weight and cardiovascular risk in the corporate setting: the GEICO study. Eur J Clin Nutrition 2013; 67:718-24. *291 GEICO employees with* ***BMI ≥ 25, type 2 diabetes, or both*** *randomized to low-fat vegan diet vs. no dietary changes for 18 weeks. Compared to the control group, vegans had greater decrease in weight (6.5 vs. 1.0 lbs, P<.001), total cholesterol (8.0 vs. 0.01 mg/dL, P<.01), LDL cholesterol (8.1 vs. 0.9 mg/dL, P<.01), and HbA1c (0.6 vs. 0.08%, P<.01). Benefits of vegan diet were more pronounced in participants who completed the trial (66% of vegans, 78% of control group).*

30. Wright N, Wilson L, Smith M, Duncan B, McHugh P. The BROAD study: a randomized controlled trial using a whole food plant-based diet in the community for obesity, ischemic heart disease, or diabetes. Nutr Diabetes 2017; 7(3):e256. doi: 10.1038/nutd.2017.3. *65 subjects aged 35-70 years who were overweight or obese and had at least 1 other chronic condition (type 2 diabetes, ischemic heart disease, hypertensions, or high cholesterol) randomized to a whole-food plant-based diet (not energy restricted) plus twice-weekly facilitated meetings vs. no dietary change for 6 months (75% completed the study). The plant-based group had 3.9 kg more reduction in body mass index*

(95% CI, 3.7 to 4.0) after 6 months, with little change at 12 months. The plant-based diet did not have a significant impact on total cholesterol levels.

Rheumatoid arthritis sample

31. Peltonen R, Nenonen M, Helve T, et al. Faecal microbial flora and disease activity in rheumatoid arthritis during a vegan diet. Br J Rheumatol 1997; 36:64-8. 43 patients with rheumatoid arthritis randomized to raw vegan diet rich in lactobacilli vs. control group (ordinary omnivorous diet) for 1 month. Vegan group showed greater rates of improvement (high- and low-improvement) and a significant diet-induced change in fecal flora.

Healthy subject sample

32. Kohnert E, Kreutz C, Binder N, et al. Changes in gut microbiota after a four-week intervention with vegan vs. meat-rich diets in health participants: a randomized controlled trial. Microorganisms 2021; 9, 727; doi.org/10.3390/microorganisms9040727. *Clinical trial of 53 healthy, omnivore, normal-weight adults (mean age 31y, 62% female) randomized to vegan diet vs. meat-rich diet for 4 weeks, with fecal samples at beginning and end of trial. The microbial composition had high intra-individual variability and overall did not differ significantly among groups at the end of the study. Most individual had similar microbiota composition at the start and end of the trial, suggesting intra-individual stability of the gut microbiotia to diet change. Limited by short-term duration of 4 weeks.*

Large Cohort Studies

China Health and Nutrition Survey

33. Zhang B, Zhai FY, Du SF, Popkin BM. The China Health and Nutrition Survey, 1989-2011. Obes Rev 2014; 15(suppl 1):2–7. *Ongoing, multipurpose, longitudinal open cohort study initiated in 1989 with follow-up every 2-4 years, with 94,532 adults from 9 provinces and 3 largest autonomous cities, providing demographic, SES, lifestyle, nutritional, and health information, plus blood samples.*

34. Li Q, Liu C, Zhang S, et al. Dietary carbohydrate intake and new-onset of hypertension: a nationwide cohort study in China. Hypertension. 2021;77:00-00. DOI: 10.1161/HYPERTENSIONAHA.120.16751. *Analysis of 12,177 adults with no baseline hypertension (HTN), of whom 4,269 developed hypertension during 95,157 person-years of follow-up, with higher risk for animal vs. plant-based diets. U-shaped association of carbohydrate intake with HTN incidence, with lowest risk at 50-55% of diet; increased risk associated with more low-quality vs. high-quality carbohydrates. Supports intake of high-quality carbohydrate, and substituting plant-based products for low-quality carbohydrates, to prevent HTN.*

The China Study

35. Campbell TC, Parpia B, Chen J. Diet, lifestyle, and the etiology of coronary artery disease: the Cornell China Study. Am J Cardiol 1998; 82:181-211. *Studied of mortality data for >50 diseases (including 7 cancers, up to 400-fold variations in geographic incidence) from 6,500 adults in 65 counties and 130 villages in rural mainland China (about 27-year time span), conducted by Cornell University, Oxford University, and Chinese Academy of Preventive Medicine, and funded by NIH and ACS. Chinese diet is typically only 10% animal products and has 3 times higher fiber than Western diet. Coronary artery disease mortality rates were inversely associated with frequency of green vegetables (r=-0.43, P<.01) and monounsaturated fatty acids (r=-0.64, P<.001) but positively associated with salt intake/urinary sodium (r=0.42, P<.01) and plasma apolipoprotein B (r=-0.37, P<.05). These apolipoproteins in turn were positively associated with meat intake (r=0.32, P<.01) and negatively associated with plant protein (r=-0.26, P<.05) and legume (r=-0.26, P<.05) intake. There was no evidence of a threshold beyond which further benefits did not accrue with increasing proportions of plant-based foods in the diet.*

36. Campbell TC, Chen J. Diet and health in rural china: lessons learned and unlearned. Nutrition Today 1999; 34:116-23. *Summary of the significant findings and rationale for the ecological, cross-sectional study (China Study) undertaken in 1983 in 65 Chinese countries to investigate association between dietary/lifestyle factors and widely varying (-10- to 400-fold) localized cancer mortality rates. Chinese diet differed from Western diet in fat (15% vs. 30-45% total energy), dietary fiber (33 vs. 10-11 g/day), and total protein (10% vs. 15-20% of total calories) intakes. Recorded 367 characteristics of diet, medical conditions, lifestyle, and disease mortality. Found that cancers, cardiovascular disease, and diabetes clustered geographically (suggesting common causes), with the strongest correlation being total cholesterol. In turn, chief determinants of increased cholesterol were intakes of fat, animal protein, and meat. Intakes of legume protein and dietary fiber were associated with lowered cholesterol. Single-factor analyses showed positive associations of lipids/fats/cholesterol with liver, colorectal, breast cancer (men and women) and all cancers (men only); and animal foods with colon cancer in men. Green vegetable intake had an inverse correlation with stomach and colon cancer. References are given to several spin-off publications with more detailed analyses.*

EPIC (European Prospective Investigation into Cancer and Nutrition) Study

37. Davey GK, Spencer EA, Appleby PN, et al. EPIC – Oxford: lifestyle characteristics and nutrient intakes in a cohort of 33,883 meat-eaters and 31,546 non meat-eaters in the UK. Public Health Nutrition 2002; 6:259-68. *Describes the EPIC-Oxford cohort as part of the European Prospective Investigation into Cancer, a cohort of over 500,000 adults recruited from 10 European countries in the 1990s. The EPIC-Oxford cohort focuses on dietary and lifestyle characteristics of 4 diet groups (N=65,429): meat-eaters (n=33,883), fish-eaters (n=10,110), lacto-ovo vegetarians (n=18,840), and vegans (n=2,596). Participants were categorized into a diet group based on responses to the following items in the questionnaire: (1) "Do you eat any meat (including bacon, ham, poultry, game, meat pies, sausages)?"; (2) "Do you eat any fish?"; (3) "Do you eat any dairy products (including milk, cheese, butter, yogurt)?"; and, (4) "Do you eat any eggs (including eggs in cakes and other baked foods)?" This study describes the cohort; subsequent publications give specific results.*

38. Appleby PN, Davey GK, Key TJ. Hypertension and blood pressure among meat eaters, fish eaters, vegetarians, and vegans in EPIC-Oxford. Public Health Nutrition 2002; 5:645-54. *Self-reported hypertension found in 15% of male meat eaters, 12% of female meat eaters, 6% of male vegans, and 8% of female vegans. Blood pressure measurements in 11,000 subjects who did not report hypertension showed that vegans had lower systolic (4.2 and 2.6 mmHg) and diastolic (2.8 and 1.7 mmHg) results compared to male and female meat-eaters, respectively.*

39. Appleby PN, Crowe FL, Bradbury KE, Travis RC, Key TJ. Mortality in vegetarians and comparable nonvegetarians in the United Kingdom. Am J Clin Nutr 2016; 103:218-30. *Analysis of 60,310 adults (34% vegetarian, 4% vegan) from the EPIC-Oxford study and Oxford Vegetarian Study (n=10,359) with 5,924 deaths in more than 1 million total years of follow-up. No difference in overall (all-cause mortality between vegetarians, vegans, regular meat eaters, low meat eaters, and fish eaters. Compared with regular meat eaters, vegetarians (including vegans) had 50% lower mortality from pancreatic cancer and cancers of the lymphatic/hematopoietic tissue. When participants were excluded if they had changed diet group at least once during follow-up in the early mortality analysis (because a change in diet could have been prompted by onset of illness), vegetarians/vegans 10% lower all-cause mortality, 20% lower mortality from malignant cancer, and 50-60% lower mortality from cancers of the lymphatic/hematopoietic tissue. No differences found between vegetarians and vegans.*

40. Bradbury KE, Crowe FL, Appleby PN, et al. Serum concentrations of cholesterol, apolipoprotein A-I, and apolipoprotein B in a total of 1,694 meat-eaters, fish-eaters, vegetarians, and vegans. Eur J Clin Nutr 2014; 68:178-83. *Cross-sectional analysis of 1,694 participants in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Oxford cohort, including 422 vegans (matched on age and sex); vegans had lowest levels of total cholesterol and apolipoprotein B than all other dietary groups, with only a small amount of the differences explained by a lower BMI among vegans.*

41. Spencer EA, Appleby PN, Davey GK, Key TJ. Diet and body mass index in 38,000 EPIC-Oxford meat-eaters, fish-eaters, vegetarians, and vegans. Int J Obes Relat Metab Disord 2003; 27:728-34. *Age-adjusted mean BMI was highest for meat-eaters (24.4 men, 23.5 women) and lowest in vegans (22.5 men, 22.0 women. Half the observed difference was explained by differences in macronutrient intake (e.g., high BMI correlated with increased protein*

and decreased fiber), but less than 5% of differences were related to lifestyle factors (e.g., smoking, physical activity, education level).

42. Papier K, Appleby PN, Fensom GK, et al. Vegetarian diets and risk of hospitalization or death with diabetes in British adults: results from the EPIC-Oxford study. Nutrition Diabetes 2019; 9:7; doi 10/1038/s41387-019-0074-0. *Prospective cohort o 45,314 adults free from diabetes at baseline followed a mean of 17.6 years, during which 1,224 cases of diabetes death/hospitalization occurred. Compared with regular meat-eaters (>50 g/day), low meat eaters (<50 g/day) were 37% less likely to develop diabetes (95% CI 25-46%), fish eaters 53% less likely (95% CI, 41-62%), and vegetarians 37% less likely (95% CI, 26-46%). The associations remained significant, but were substantially attenuated after adjusting for body mass index (BMI).*

43. Tong TYN, Appleby PN, Armstrong MEG, et al. Vegetarian and vegan diets and risk of total and site-specific fractures: results from the prospective EPIC-Oxford study. BMC Medicine 2020; 18:353. doi: 10.1186/s12916-020-01815-3 . *Cohort study of 29,380 meat eaters, 8,037 fish eaters, 15,499 vegetarians, and 1,982 vegans followed for mean of 18 years with 3,941 total fractures. Compared with meat eaters, adjusted hazard ratios (HR) for hip fracture were higher in fish eaters (HR 1.26, 95% CI 1.02-1.54), vegetarians (1.25, 1.04-1.50), and vegans (2.31, 1.66-3.22); vegans also had higher risks of total (1.43, 1.20-1.70), leg (2.05, 1.23-3.41), and other main site fractures (1.59, 1.02-2.50 compared to meat eaters. Remained significant, but somewhat reduced, after adjustment for dietary calcium and total protein.*

Lifetime Risk Pooling Project

44. Wilkins JT, Karmali KN, Huffman MD, et al. Data resource profile: the cardiovascular disease lifetime risk pooling project. Int J Epidemiol 2015; 1557-64. *Although not undertaken with a primary intent of dietary analysis, baseline data is available on many of the included cohorts and has been used to analyze risk of incident cardiovascular disease (CVD) and all-cause mortality (see below). This dataset includes over 225,000 unique individuals from 20 prospective, community-based cohort studies (including Framingham) with long-term follow-up data collected between 1948-2010. Information about risk status, demographics, medications, health behaviors, smoking status assessed at baseline and in many studies with repeated measures and outcomes were ascertained using national databases, Medicare claims, and direct review of medical records.*

45. Zhong VW, Van Horn L, Cornelis MC, et al. Associations of dietary cholesterol or egg consumption with incident cardiovascular disease (CVD) and mortality. JAMA 2019; 321:1081-95. *Analysis of 29,615 participants from 6 cohorts (median 17.5y follow-up) with dietary information and no baseline CVD from the Lifetime Risk Pooling Project. Each additional 300 mg of dietary cholesterol/day was associated with an adjusted increase of 17% in CVD (95% CI, 2-26%) and 18% in all-cause mortality (95% CI, 10-26%). Each additional half an egg/day was associated with an adjusted increase of 6% in CVD (95% CI, 3-10%) and 8% in all-cause mortality (95% CI, 4-11%), but were no longer significant after adjusting for dietary cholesterol consumption. Recommend that dietary guidelines and updates consider the dose-response relationship of dietary cholesterol and eggs on CVD and all-cause mortality.*

NurtiNet-Santé Study

46. Alles B, Baudry J, Mejean C, et al. Comparison of sociodemographic and nutritional characteristics between self-reported vegetarians, vegans, and meta-eaters from the NurtiNet-Santé Study. Nutrients 2017; 9:1023; doi:10/3390/nu9091023. *Study of 93,823 French adults (96.6% meat-eaters, 2.5% vegetarians, 0.8% vegans), from a web-based cohort study launched in 2009. Participants completed 3 web-based 24-hour dietary records. Compared with meat-eaters, vegetarians had a higher educational level and were more likely to be female, younger, and self-employed. Vegetarians had the most balanced diets and better adherence to French dietary guidelines, whereas vegans had highest fiber intake (53% above 30g/day vs. 11% of meat-eaters and 28% of vegetarians), but also a higher prevalence of vitamin B12 inadequacy. Conclude that only self-reported vegetarians and vegans may meet nutritional recommendations.*

47. Kane-Diallo A, Srour B, Sellem L, et al. Association between a pro plant-based dietary score and cancer risk in the prospective NutriNet-santé cohort. Int J Cancer 2018; 143(9):2168-2176. doi:

10.1002/ijc.31593. Epub 2018 Aug 7. *Prosopective cohort of 42,544 adults aged 45y or older who complete at least 3 24-hour dietary records during the 1st year of follow-up, with 1,591 new cancer cases (including 487 breast, 243 prostate, 198 digestive, 68 lung) diagnosed during follow-up (2009-2016). A higher pro plant-based dietary score was associated with decreased overall cancer risk (hazard ratio 0.85, 95% CI 0.76 to 0.97), decreased digestive cancer risk (hazard ratio 0.68, 95% CI, 0.47 to 0.99), and decreased lung cancer risk (hazard ratio 0.47, 95% CI 0.25 to 0.90). There were no associations between dietary score and breast or prostate cancers.*

PREDIMED Study: Prevención con Dieta Mediterránea

48. Martinez-González MA, Sánchez-Tainta A, Corella D, et al. A provegetarian food pattern and reduction in total mortality in the Prevención con Dieta Mediterránea (PREDIMED) study. Am J Clin Nutr 2014; 100(Suppl 1): 320S-8S. *Prospective cohort of 7,216 participants (mean age 67 years), enrolled from 2003-2009, at high cardiovascular risk received a validated 137-item food-frequency questionnaire at baseline then yearly for a median of 4.8 years (323 deaths: 76 cardiovascular, 130 cancer, 117 other). Fruit, vegetables, nuts, cereals, legumes, olive oil, and potatoes were positively weighted for the provegetarian food pattern (PFP, range 12-60 points); added animal fats, eggs, fish, dairy products, and meats or meat products were negatively weighted. A PFP ≥ 40 points reduced mortality when compared to a PFP < 30 points (adjusted hazard ratio 0.59, 95% CI 0.40 to 0.88); similar results were found when using updated information on diet (relative risk 0.59, 95% CI, 0.39 to 0.89).*

PURE (Prospective Urban Rural Epidemiology) Study

49. Dehghan M, Mente A, Zhang X, et al. Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five contents (PURE): a prospective study. Lancet 2017; 390:2050-62. *Multi-national cohort study of 135,335 individuals aged 35-70 years without cardiovascular disease enrolled from 2003-13 from 18 low-, middle-, and high-income countries (7 geographical regions: North America/Europe, South America, Middle East, south Asia, China, southeast Asia, and Africa) with 5,796 total deaths (1,649 cardiovascular deaths) and 4,784 major cardiovascular events between 2003 and 2018 (median 7.4 years follow-up). Higher carbohydrate intake (5th quintile vs. 1st quintile) increased total mortality (hazard ratio 1.28, 95% CI 1.12 to 1.46), but no distinction was made between whole grains and refined carbohydrates (which predominate in low- and middle-income countries). Higher fat intake (5th quintile vs. 1st quintile) reduced total mortality (HR 0.77, 95% CI, 0.67 to 0.87) with similar findings for fat types (saturated, monounsaturated, and polyunsaturated). Total fat, saturated fat, and unsaturated fats were not associated with myocardial infarctions or cardiovascular mortality.*

50. Dehghan M, Merite A, Rangarajan S, et al. Association of dairy intake with cardiovascular disease and mortality in 21 countries from five continents (PURE): a prospective cohort study. Lancet 2018; 392:2288-97. *Multi-national cohort study of 136,384 individuals aged 35-70 years without cardiovascular disease from 21 low-, middle-, and high-income countries (originally 18, but 3 joined later), with 10,567 major cardiovascular events or mortalities between 2003 and 2018. Higher dairy intake >2 servings per day compared to no intake was associated with lower risk of composite mortality/events (hazard ratio 0.84, 95% CI 0.75 to 0.94 for all dairy; HR 0.71, 95% CI 0.60 to 0.83 if only whole fat dairy), total mortality (HR 0.83, 95% CI, 0.72 to 0.96), non-cardiovascular mortality (HR 0.86, 95% CI 0.72 to 1.02), and stroke (HR 0.66, 95% CI 0.53 to 0.82). Higher milk intake >1 serving per day vs. no intake was associated with lower composite mortality/events (HR 0.90, 95% CI, 0.82 to 0.99) and yogurt intake >1 serving per day also had lower composite mortality/events (HR 0.86, 95% CI 0.75 to 0.99). No significant associations found between outcomes and higher intakes of butter or cheese.*

51. Miller M, Mente A, Dehghan M, et al. Fruit, vegetable, and legume intake, and cardiovascular disease and deaths in 18 countries (PURE): a prospective cohort study. *Lancet 2017; 390:2037-49. Multi-national cohort study of 135,335 individuals aged 35-70 years without cardiovascular disease from 18 low-, middle-, and high-income countries (7 geographical regions: North America/Europe, South America, Middle East, south Asia, China, southeast Asia, and Africa) with 5,796 total deaths (1,649 cardiovascular deaths) and 4,784 major cardiovascular events between 2003 and 2018 (median 7.4 years follow-up). Higher total fruit, vegetable, and legume intake was associated with lower total mortality (hazard ratio 0.81, 95% CI 0.68 to 0.96) and lower non-cardiovascular mortality (HR 0.84, 95% CI 0.68 to 1.04, P=.004). Optimal benefit for total mortality seen with 3-4 servings per day (HR 0.78, 95% 0.69 to*

0.88), with no change for higher consumption. Similar results for individual analyses of fruits, vegetables, and legumes, but raw vegetables had more benefits than cooked vegetables.

52. Mente A, O'Donnell M, Rangarajan S, et al. Urinary sodium excretion, blood pressure, cardiovascular disease, and mortality: a community-level prospective epidemiological cohort study. Lancet 2018; 392:496-506. *Multi-national cohort study (PURE) of 95,767 adults age 35-70 years, without cardiovascular disease, from 18 countries. Sodium intake increased the risk of cardiovascular disease and strokes only in communities where mean intake was greater than 5 g/day; no consistent associations seen below this consumption level.*

Rotterdam Study

53. Alferink LJM, Erler NS, de Knegt RJ, et al. Adherence to a plant-based, high-fibre dietary pattern is related to regression of non-alcoholoc fatty liver disease (NAFLD) in an elderly population. Eur J Epidemiol 2020; 35:1069-85. *Cohort of 963 elderly adults of whom 343 had NAFLD diagnosed by abdominal ultrasonography, with median 4.4y follow-up, during which 5% had new incident NAFLD and 30% had regression of baseline NAFLD. Adherence to a plant-based, high-fiber and low-fat diet was related to regression of NAFLD.*

54. Chen Z, Zuurmond MG, van der Schaft N, et al. Plant versus animal-based diets and insulin resistance, prediabetes, and type 2 diabetes: the Rotterdam Study. Eur J Epidemiol 2018; 33:883-93. *Long-term follow-up study of 6,798 adults (mean age 63 years) in a prospective, population-based cohort study with dietary intake data collected at baseline and 3 sub-cohorts (1989-93, 2000-01, and 2006-08). A continuous plant-based dietary index (PBDI), range 0-92, was used to assess adherence to a plant-based vs. animal-based diet. After adjusting for lifestyle and sociodemographic factors, a higher PBDI was associated with lower insulin resistance, lower prediabetes risk (hazard ratio 0.89, 95% CI 0.81 to 0.98), and lower type 2 diabetes risk (hazard ratio 0.82, 95% CI 0.73 to 0.92). After additional adjustment for body mass index, the association with insulin resistance remained significant but not for prediabetes risk.*

55. Chen Z, Schoufour JD, Rivadeneira F, et al. Plant-based diet and adiposity over time in a middle-aged and elderly population: the Rotterdam Study. Epidemiology. 2018 Nov 30. doi: 10.1097/EDE.0000000000000961. *Follow-up of 9,633 adults, with data collection (anthropometrics and body composition) every 3 to 5 years from 1989 to 2016 (median 7.1 years), showed that participants with a 10 point higher score on the plant-based dietary index score (range 0 to 92) a lower BMI by 0.70 kg/m over the study period (95% CI 0.59 to 0.81), lower waist circumference by 2.0 cm (95% CI, 1.7 to 2.3), lower fat mass index by 0.66 kg/m (95% CI, 0.52 to 0.80), and lower body fat percentage by 1.1 points (95% CI 0.84 to 1.10).*

Seventh-Day Adventist Cohort Studies

56. [Adventist Mortality Study]. Kahan HA, Phillips RL, Snowdon DA, Choi W. Association between reported diet and all-cause mortality. Twenty-one year follow-up on 27,530 adult Seventh-day Adventists. Am J Epidemiol 1984; 119:775-87. *Long-term follow-up on original study conducted between 1960 and 1966, by matching food consumption at beginning of study with death certificates for 1960 to 1980. All-cause mortality was significantly reduced with green salad consumption and increased for eggs and meat, when adjusted for age, sex, smoking history, history of major chronic disease, and age at initial exposure to the Adventist Church. This is one of many studies that have been published based on this cohort.*

57. [Adventist Health Study 1]. Beeson WL, Mills PK, Phillips RL, Andress M, Fraser GE. Chronic disease among Seventh-day Adventists, a low-risk group: rationale, methodology and description of the population. Cancer 1989; 64:570-81. *Describes cohort of 34,198 Adventists (55% lacto-ovovegetarian) age 30y or older, enrolled in 1976 and followed for 6 years, with reports on all-cause mortality for 8 years (1975-82) and incident cancers and ischemic heart disease (1977-82). Subsequent analyses give specific findings based on dietary patters (e.g., vegan vs. vegetarian vs. ominivorous).*

58. [Adventist Health Study 2]. Butler TL, Fraser GE, Beeson WL, et al. Cohort profile: the Adventist Health Study-2 (AHS-2). Int J Epidemiol 2008; 37:260-5. *Large cohort study designed to investigate role of foods, nutrients, lifestyle factors, and metabolic risk indicators in cancer causation, especially breast, colon, and prostate. Recruited*

96,000 Seventh-day Adventists age 30y or older from 2002 through 2007. Dietary pattern definitions were based on measured foot intake rather than self-identification of dietary patterns. Multiple subsequent publications report findings.

59. Orlich MJ, Singh PN, Sabate J, et al. Vegetarian dietary patterns and mortality in Adventist Health Study 2. JAMA Intern Med 2013; 173:1230-8. *Analysis of 2,570 deaths from a subset of 73,308 participants from the AHS-2 study (mean follow-up 5.8 years) should 12% decrease in adjusted all-cause mortality (95% CI, 3-20%) for all vegetarians vs. nonvegetarians. Greater decrease for men (18%, 95% CI, 6-28%) than for women (7%, -5 to 18%). Vegetarian diets also had lower cardiovascular mortality, noncardiovascular noncancer mortality, renal mortality, and endocrine mortality. The lack of similar results with the EPIC-Oxforsd cohort could be because AHS-2 participants consumed less saturate fat, twice as much fiber, and were generally nonsmokers and nondrinkers.*

Singapore Chinese Health Study

60. Hankin JH, Stram DO, Arakawa K, et al. Singapore Chinese Health Study: development, validation, and calibration of the quantitative food frequency questionnaire. Nutr Cancer. 2001; 39:187–195. *Describes the cohort of 63,257 Chinese persons aged 45–74 years (citizens or permanent residents) enrolled between 1993 and 1998, with in-person interviews at recruitment to collect information on habitual diet (165-item food frequency questionnaire), demographic factors, height, weight, tobacco use, physical activity, female menstrual and reproductive, history, and medical history. The first and second follow-up interviews were conducted by telephone calls made during 1999–2004 and 2006–2010, respectively, with a participation rate of 89.9% for the first follow-up and 81.9% for the second follow-up.*

61. Chen GC, Koh WP, Neelakantan N, et al. Diet quality indices and risk of type 2 diabetes mellitus: the Singapore Chinese Health Study. Am J Epidemiol 2018; 187; 12: DOI: 10.1093/aje/kwy183. *Subset of 45,411 adults (aged 45-74 years) from the Singapore Chinese Health Study – who were free of diabetes, cancer, and cardiovascular disease at baseline (1993-1998) – followed through 2010 (median 11.1 years) for type 2 diabetes diagnosis. Dietary pattern scores for the highest vs. lowest quintile showed reduced incidence of diabetes for the alternate Mediterranean diet (aMED) of 16% (95% CI, 8-23%) for the Alternate Healthy Eating Index 2010 of 21% (95% CI, 13-27%), for the Dietary Approaches to Stop Hypertension (DASH) diet of 29% (95% CI, 21-35%), an overall plant-based index of 6% (95% CI, 3-8%), and for a healthful plant-based index of 7% (95% CI, 5-10%).*

62. Wu J, Song X, Chen GC, et al. Dietary pattern in midlife and cognitive impairment in late life: a prospective study in Chinese adults. Am J Clin Nutr. 2019 Aug 2. pii: nqz150. doi: 10.1093/ajcn/nqz150. [Epub ahead of print]. *Cohort of 16,498 adults frm the Singapore Health Study aged 45-74 years at baseline (1993-1998) re-interviewed at a 3rd follow-up visit about 20 years later (2014-2016). Cognitive impairment was present in 14.4% of participants (using the Mini-Mental State Examination) and was consistently lower for highest vs. lowest quintile of healthy dietary patterns: 33% lower with alternate Mediterranean diet (95% CI, 23-41%), 25% for the Dietary Approaches to Stop Hypertension (DASH) diet (95% CI, 15-34%), 18% for the Alternative Healthy Eating Index (95% CI, 6-29%), and 22% lower for the healthy plant-based diet index (95% CI, 10-32%). Overall, a 1 standard deviation increase in diet quality scores was associated with 7-16% lower risk of cognitive impairment.*

Tzu Chi Health Study, Taiwan

63. Chang CM, Chiu THT, Chang CC, Ming-Nan L, Lin CL. Plant-based diet, cholesterol, and risk of gallstone disease: a prospective study. Nutrients 2019, 11, 335; doi:10.3390/nu11020335. *Analysis of 4,839 participants with 29,295 person-years of follow-up from the Tzu Chi Health Study, which included 6,002 participants (ages 18-87 years) recruited from 2007-2009, primarily (77%) from a Buddhist Hospital. A Food Frequency Questionnaire and dietary questionnaire were used to assess intake and participants were encouraged, but not required, to become vegetarians. Vegetarian diet reduced risk of symptomatic gallstone disease by 48% in women (HR 0.52, 95% CI, 0.28-0.96), but not in men, compared with non-vegetarian diet, adjust for age, education, smoking, alcohol, physical activities, diabetes, kidney diseases, BMI, lipid-lowering medication, and hypercholesterolemia. Women non-vegetarians with high cholesterol had 3.8 times risk of gallstone disease (HR 3.81, 95% CI 1.61-9.01) compared with vegetarians with normal cholesterol.*

64. Chiu THT, Chang CC, Lin CL, Lin MN. A vegetarian diet is associated with a lower risk of cataract, particularly among individuals with overweight: a prospective study. J Acad Nutr Diet 2020; Dec 11;S2212-2672(20)31428-3. doi: 10.1016/j.jand.2020.11.003. *Cohort of 4,450 adults from the Tzu Chi Health Study, age 40y or older and without cataracts at recruitment, followed 5-7 years with 476 incident cases of cataracts with 25,103 person-years of follow-up. Vegetarian diet had adjusted 20% reduced cataract risk (HR 0.80, 95% CI, 0.65 to 0.99, P=.04); more pronounced if overweight (HR 0.70, 95% CI 0.50 to 0.99, P=.04).*

65. Chiu THT, Liu CH, Chang CC, et al. Vegetarian diet and risk of gout in two separate prospective cohort studies. Clin Nutrition 2019; doi.org/10.1016/j.clnu2019;03;016. *Analysis of 4,903 participants in the Tzu Chi Health Study (recruited 2007-2009) and 9,032 participants in the Tzu Chi Vegetarian Study (recruited 2005) assess with a dietary and food frequency questionnaire, with gout incidence assessed through national health insurance database. Vegetarians had lower uric acid than non-vegetarians and had 77% lower risk of gout (95% CI, 21-86%) in the first cohort and a 39%% lower risk in the second (95% CI, 12-59%).*

66. Shen Y, Chang C, Lin M, Lin C. Vegetarian diet is associate with lower risk of depression in Taiwan. Nutrients 2021; 13, 1059; doi.org/10.3390/nu13041059. *Prospective cohort of 12,062 Buddhist volunteers age 20y of older (mean age 51y, 68% female) without depression, who had quit smoking and drinking for at least 2 years, and were "encouraged to consume a vegetarian diet as frequently as possible" (in accordance with Buddhist teachings of environmental conservation and compassion to animals). Diet assessed with 57-item food frequency questionnaire, yielding 3,571 vegetarians and 7,006 non-vegetarians. Vegetarian group had lower incidence of depressive disorders (2.4 vs. 3.2 per 10,000 person-years) or a 30% decrease (HR 0.70, 95% CI 0.52 to 0.93). Generalizability may be limited.*

UK Biobank Resource

67. Bycroft C, Freeman, C, Petkova D, et al. The UK Biobank resource with deep phenotyping and genomic data. Nature 2018; 562:203-9. *Cohort of 500,000 individuals aged 40-69 at recruitment (2006 to 2010) with rich variety of phenotypic and health-related information is available on each participant, including biological measurements, lifestyle indicators, biomarkers in blood and urine, and imaging of the body and brain. Follow-up information is provided by linking health and medical records. Genome-wide genotype data have been collected on all participants, providing many opportunities for the discovery of new genetic associations and the genetic bases of complex traits.*

US Healthcare Worker Studies (Nurses and Health Professionals)

68. Baden MY, Liu G, Satija A, et al. Changes in plant-based diet quality and total and all cause-specific mortality. Circulation 2019; 140:979-91. *Cohort of 49,407 women from the Nurses' Health and 25,907 men from the Health Professionals Follow-up Study, free from cardiovascular disease (CVD) and cancer in 1998, followed through 2014 (90% follow-up), during which there were 10,686 deaths (2,046 CVD, 3,091 cancer). Compared with participants whose plant-based diet indices (PDI's) were stable, those with a more healthful PDI had 10% lower total mortality (95% CI, 5-15%) and those with an unhealthful PDI had 12% higher mortality (95% CI, 7-18%). For CVD, a healthful PDI lowered mortality by 9% (95% CI, 4-14%) and an unhealthful PDI increased mortality by 8% (95% CI, 2-14%). No consistent associations were seen between PDIs and cancer mortality.*

69. Chen Z, Drouin-Chartier JP, Li Y, et al. Changes in plant-based diet indices and subsequent risk of type 2 diabetes in women and men: three U.S. prospective cohorts. Diabetes Care 2021; 44:663-71. *Prospective chohort of 76,530 women in Nurses' Health Study (NHS), 81,569 in NHS II, and 34,468 men in the Health Professionals Follow-up Study, with 12,627 cases of type 2 diabetes documented in 2,955,350 person-years of follow-up. Those with the largest decrease (>10%) in the Plant-based Diet Index and the healthful PDI over 4 years had 12-23% higher diabetes risk in subsequent 4 years (adjusted for alcohol, smoking, physical activity, BMI, and other factors). Weight changes accounted for 6-36% of the associations between changes in PDI and diabetes risk.*

70. Satija A, Bhupathiraju SN, Spiegelman D, et al. Healthful and unhealthful plant-based diets and the risk of coronary artery heart disease in US adults. J Am Coll Cardiol 2017; 70:411-422. *Pooled analysis of 73,710 women from the Nurses' Health Study (1984-2012), 92,329 women from the Nurses' Health Study 2 (1986-2012), and 43,259 men in the Health Professionals follow-up study (1986-2012) who were free of chronic disease at baseline. A*

plant-based diet index (PDI) score was created, with higher scores for healthy plant foods (e.g., whole grains, fruits, vegetables, nuts, legumes, oils) and lower scores for less healthy foods (juices, sweetened beverages, refined grains, potatoes, fried food, sweets) and for animal foods. There were 8,631 coronary heart disease (CHD) incidents over 4.8 million person-years of follow-up. A high PDI reduced risk of CHD by 25% (hazard ratio 0.75, 95% CI 0.68 to 0.83, p trend <.001) and a low (unhealthy) PDI increased risk by 32% (HR 1.32, 95% CI 1.20 to 1.46, p trend <.001). Conclude that higher plant-based intake substantially lowers CHD risk.

71. Satija A, Bhupathiraju SN, Rimm EB, et al. Plant-based dietary patterns and incidence of type 2 diabetes in US men and women: results from three prospective cohort studies. PLoS Med 2016; 14:13(6):e1002039. *Pooled analysis of 69,949 women from the Nurses' Health Study (1984-2012), 90,239 women from the Nurses' Health Study 2 (1991-2011), and 40,539 men from the Health Professionals Follow-Up Study (1986-2010) who were free of chronic disease from baseline. A plant-based diet index (PDI) score was created, with higher scores for healthy plant foods (e.g., whole grains, fruits, vegetables, nuts, legumes, oils) and lower scores for less healthy foods (juices, sweetened beverages, refined grains, potatoes, fried foods, sweets) and for animal foods. There were 16,162 new cases of type 2 diabetes during 4.1 million person-years of follow-up. Looking at extreme deciles, a high PDI reduced incidence of type 2 diabetes by 49% (hazard ratio 0.51, 95% CI, 0.47 to 0.55, p trend <.001) and a low (unhealthy) PDI increased risk by 16% (HR 1.16, 95% CI 1.08 to 1.25, p trend <.001). The impact of a high PDI on diabetes decreased from 49% to 20% after adjusting for body-mass index; the impact of an unhealthy PDI was unchanged. Conclude that higher plant-based intake substantially lower risk of developing type 2 diabetes.*

72. Satija A, Malik V, Rimm EB, et al. Changes in intake of plant-based diets and weight change: results from 3 prospective cohort studies. Am J Clin Nutr 2019 May 25. pii: nqz049. doi: 10.1093/ajcn/nqz049. [Epub ahead of print]. *Pooled analysis of 126,982 adults from the Nurses' Health Study (NHS), NHS2, and the Health Professionals Follow-Up Study assessed for weight gain over 4 years (about 1.5 kg). After adjusting for other lifestyle factors, a 1-SD in plant-based diet index (PDI) emphasizing healthy foods (whole grains, fruits/vegetables, nuts/legumes, vegetable oils, tea/coffee) resulted in 0.68 kg less weight gain (95% CI, 0.66-0.69, P<.001), but an unhealthy PDI (refined grains, potato/fries, sweets, sweetened drinks/juices) resulted in 0.36 kg more weight gain (95% CI, 0.34 to 0.37, P<.001).*

73. Song M, Fung TT, Hu FB, et al. Association of plant protein intake with all-cause and cause-specific mortality. JAMA Int Med 2016; 176:1453-63. *Analysis of 131,342 participants (65% women, mean age 49 years) from the Nurses' Health Study (121,700 US female nurses from 1980 to 2012) and the Health Professionals Follow-up Study (51,529 US male health professional from 1986-2012). Participants rated by survey every 2 years how often, on average, they consumed standard portions of different foods in the prior year, from which the investigators calculated protein (animal vs. plant) as percent of total energy consumption. For participants with at least 1 unhealthy lifestyle factor (e.g., smoking heavy alcohol, overweight/obesity, physical inactivity) a higher plant protein intake significantly reduced all-cause mortality and cardiovascular mortality (adjusted for lifestyle and dietary risk) and a higher animal protein intake significantly increased cardiovascular mortality (but not all-cause mortality). When 3% of animal protein was replaced with plant protein, all-cause mortality fell by 34% if processed red meat was replaced, 19% when eggs were replaced, and 12% when unprocessed red meat was replaced.*

Miscellaneous Cohort Studies

74. Keaver L, Ruan M, Chen F, et al. Plant- and animal-based diet quality and mortality among US adults: a cohort study. Br J Nutr 2020 Sep 18;1-11. doi: 10.1017/S0007114520003670. *Cohort of 36,825 US adults in the National Health and Nutrition Examination Survey 1999-2014 with median 8.3y follow-up with 4,669 all-cause deaths (798 from heart disease, 1,021 from cancer). Calculated 3 Diet Quality Indices (DQI): comprehensive (cDQI), plant-based (pDQI), and animal based (aDQI). Highest quartile of cDQI had 25% lower all cause mortality (HR 0.75, 95% CI 0.65 to 0.86), largely due to reduced mortality from highest vs. lowest quartile pDQI)HR 0.66, 95% CI, 0.58 to 0.74); no independent association found for the quality of animal foods (aDQI) and mortality.*

75. Kim H, Lee K, Rebholz CM, Kim J. Plant-based diets and incident metabolic syndrome (MetS): results from a South Korean prospective cohort study. PLoS Med. 2020;17:e1003371. doi: 10.1371/journal.pmed.1003371. *NB: Metabolic syndrome (MetS) is centripetal obesity plus HTN, high blood sugar,*

and high cholesterol/triglycerides (increases risk of stroke, heart disease, and type 2 diabetes). Cohort of 5,646 adults, age 40-69y without MetS or related chronic diseases at baseline, followed 8 years with 2,583 cases of MetS; 50% higher risk for highest vs. lowest quintile of unhealthy plant-based diet index (refined carbohydrates, sugars, salty foods) (HR 1.50, 95% CI 1.311.71), decreasing slightly when adjusted for BMI.

76. Kim H, Caulfield LE, Garcia-Larsen V, et al. Plant-based diets are associated with a lower risk of incident cardiovascular disease, cardiovascular disease mortality, and all-cause mortality in a general population of middle-aged adults. J Am Heart Assoc. 2019 Aug 20;8(16):e012865. doi: 10.1161/JAHA.119.012865. Epub 2019 Aug 7. *Cohort of 12,168 adults in the Atherosclerosis Risk in Communities study followed from 1987 through 2016. Cox regression analysis showed participants in the highest vs. lowest quintile for adherence to overall plant-based diet index or pro-vegetarian diet had 16% lower risk of cardiovascular disease, 31-32% less CVD mortality, and 18-25% less all-cause mortality. A higher plant-based diet index has 19% less CVD mortality and 11% less all-cause mortality, but no association with incident cardiovascular disease.*

77. Lee K, Kim H, Rebholz CM, Kim J. Association between different types of plant-based diets and risk of dyslipidemia: a prospective cohort study. Nutrients 2021; 13: doi: 10.3390/nu13010220. *Cohort of 4,507 Korean adults 40y or older, without baseline dyslipidemia or related chronic diseases, drawn from the Korean Genome and Epidemiology Study (10,030 participants) followed for 14 years, during which 2,995 incident dyslipidemia cases occurred. Strong associations of dyslipidemia with healthful plant-based diet index (lowest vs. highest quintile, hazard ratio 0.63) and with unhealthy plant-based diet index (HR 1.48); health plant-based index was associated with lower risk for all lipid disorders.*

78. Romanos-Nanclares A, Toledo E, Sanchez-Bayona R, et al. Healthful and unhealthful provegetarian food patterns and the incidence of breast cancer: results form a Mediterranean cohort. Nutrition 2020; 79-80:110884. doi: 10.1016/j.nut.2020.110884. *Cohort 0f 10,812 women in the Seguimeinto Universidad de Navarra study followed median 11.5y with 101 incident breast cancer cases. Inconsistent associations of high- vs. low-quality provegetarian dietary patterns with breast cancer incidence; 45% lower incidence for tertile 2 vs. tertile 1 provegetarian dietary patterns (HR 0.55, 95% CI, 0.32 to 0.95), but no associations for highest tertile.*

79. Shu X, Calvert JK, Cai H, et al. Plant and animal protein intake and risk of incident kidney stones: results from the Shanghai men's and women's health studies. J Urol. 2019 Aug 20:101097JU0000000000000493. doi: 10.1097/JU.0000000000000493. [Epub ahead of print]. *Follow-up of 2,653 adults showed that participants in the highest quintiles of animal and nondairy animal protein intake had increased risk for kidney stones compared to lower quintile (hazard ratio 1.16, 95% CI, 1.01 to 1.32). The highest intake quintiles of animal-to-plant protein ratios and nondairy animal-to-plant protein ratios had similar findings.*

80. Yishahak SF, Hinkle SN, Mumford SL, et al. Vegetarian diets during pregnancy, and maternal and neonatal outcomes. In J Epidemiol 2021, 165-178. *Cohort of 1,948 low-risk pregnant women with 32 vegetarians, 7 pesco-vegetarians, and 301 semi-vegetarians; full vegetarians had increased odds of neonates small for gestational age (adjusted OR 2.51, 95% CI, 1.01 to 6.21) but without any morbidity.*

81. Wang H, Huang L, Lin L, et al. The overall plant-based diet index during pregnancy and risk of gestational diabetes mellitus: a prospective cohort study in China. Br J Nutr 2021; 20: doi: 10.1017/S0007114521000234. *Dietary data from Tongji Maternal and Child Health Cohort collected at baseline and 13-28 weeks of pregnancy for 2,099 women, of whom 169 were diagnosed with gestational diabetes; plant-based dietary index (PDI) reduced odds of diabetes by 57% for highest vs. lowest quartile, with each quartile increment reducing odds by 29%. Conclude that a plant-based diet could reduce gestational diabetes risk during pregnancy.*

Intervention Studies Without a Comparison or Control Group

Coronary Artery Disease

82. Esselstyn CB Jr, Ellis SG, Medendorp SV, Crowe TD. A strategy to arrest and reverse coronary artery disease: a 5-year longitudinal study of a single physician's practice. J Fam Pract 1995; 41:560-8. *Cohort of 22 patients with angiographically documented, severe coronary artery disease who took cholesterol-lowering drugs and followed a plant-based diet with <10% fat. 5 patients dropped out within 2 years, 17 maintained the diet (mean 5.5 years follow-*

up). Cholesterol reduced from mean 246 mg/dl to 150 mg/dl. Of 25 cardiac lesions, 11 regressed and 14 remained stable. For the 11 subjects remaining after 10 years all had arrest of disease and none had new infracts.

83. Esselstyn CB Jr. Updating a 12-year experience with arrest and reversal therapy for coronary hear disease. Am J Cardiol 1999; 84:339-41. *Cohort of 24 adults (23 men, 1 woman) with severe, angiographically demonstrated coronary artery disease (but all non-smoking, non-hypertensive, non-diabetic) who agreed to follow a plant-based diets with <10% of calories from fat (no oil, but did allow skim milk and no-fat yogurt); 18 patients adhered to the diet and 6 were dropped from the study after 12-18 months. After 5 years, 11/18 in the adherent group had angiography, showing disease arrest in 100% and regression in 8 (73%). Adherent patients after 12 years had no extension of clinical disease, no coronary events, and no interventions, despite having 49 coronary events in the 8 years before the study. Mean total cholesterol was 145 mg/dl.*

84. Esselstyn CB Jr, Gendy G, Doyle J, Golubic M, Roizen MF. A way to reverse coronary artery disease? J Fam Pract 2014; 63:-63. *Cohort study of 198 consecutive, self-selected nonsmoking adults (91% male) with multiple comordibities (hyperlipdemia 161, hypertension 60, diabetes 23) who voluntarily asked for counseling in plant-based nutrition (whole-food, plant-based diet with no added oil, salt, sugar or processed foods) for disease treatment and were followed for a mean of 44 months (patients were encouraged to exercise and were later asked to avoid caffeine and fructose). Patients who adhered (e.g., avoided all meat, fish, dairy, and added oils) to the diet (89%) did better than those who did not (11%) in terms of symptom reduction (94% vs. 0%), disease reversal (22% vs. 0%), and adverse events (0.6% vs. 62%) (e.g., sudden cardiac death, heart transplant, ischemic stroke, coronary artery bypass surgery). Although the results are impressive, generalizability is limited by self-selection, reliance on patient history for baseline conditions (e.g., no angiogram as in prior study), and telephone follow-up to assess outcomes and results.*

Fibromyalgia

85. Kaartinen K, Lammi K, Hypen M, et al. Vegan diet alleviates fibromyalgia symptoms. Scand J Rheumatol 2000; 29:308-13. Comparative (non-randomized) study of 33 patients with fibromyalgia on an uncooked vegan diet vs. omnivorous diet for 3 months. Vegan group had significant reductions in pain, joint stiffness, BMI, and serum cholesterol; and significant improvements in quality of sleep, general health, and overall rheumatology symptoms.

Rheumatoid arthritis

86. McDougall J, Bruce B, Spiller G, Westerdahl J, McDougall M. Effects of a very low-fat, vegan diet in subjects with rheumatoid arthritis. J Altern Complement Med 2002; 8:71-5. *24 patients (mean age 56 years) with moderate-to-severe rheumatoid arthritis (RA) placed on a low-fat (10%) vegan diet for 4 weeks. All measures of RA symptomatology decreased significantly, except for morning stiffness. CRP and RA factor decreased; ESR was unchanged.*

Influential Books

1. Buettner D. The Blue Zones, 2nd ed. Washington, DC: National Geographic; 2012.
2. Campbell TC, Campbell TM II. The China Study: The Most Comprehensive Study of Nutrition Ever Conducted and the Startling Implications for Diet, Weight Loss and Long-Term Health. Dallas: Benbella Books; 2006.
3. Esselstyn CB Jr. Prevent and Reverse Heart Disease: The Revolutionary, Scientifically Proven, Nutrition-Based Cure. New York: Penguin Group; 2007.
4. Frazier M, Cheeke R. The Plant Based Athlete: A Game-Changing Approach to Peak Performance. New York: HarperOne; 2021.
5. Greger M, Stone G. How Not to Die: Discover the Foods Scientifically Proven to Prevent and Reverse Disease. New York: Flatiron Books; 2015
6. Stone G. Forks Over Knives: The Plant-Based Way to Health. New York: The Experiment, LLC; 2011.

Prevalence data: Radnitz C, Beezhold B, DiMatteo J. Investigation of lifestyle choices of individuals following a vegan diet for health and ethical reasons. Appetite 2015; 90:31-6.

- ✓ US population 1997: 300-500,000 vegans; about 0.11 to 0.19% population
- ✓ US population 2012: 2.5-6.0 million vegans; about 1-2% population (about 10-fold increase in 15 years)
- ✓ Other countries: Israel 5% vegans, UK 2%, Australia 1%, Germany 1%
- ✓ India: 31% vegetarians, but relatively few vegans

Google trends: Use of "vegan" as search term has increased 6-fold from 2004 to 2017, and 2-fold from 2015 to 2017; relatively stable since 2017. Top search locations are Australia, Canada, New Zealand, US, and UK.

Quotations of Note

From TC Campbell: Nutritional renaissance and public health policy. J Nutr Biol 2017; 3:124-38.

"The health benefits associated with whole plant-based foods are not sufficiently proven for many people. Thus I suggest that the evidence supporting the health value of a whole food diet be considered a hypothesis, not proven fact. For me, this evidence is more than convincing enough to make major decisions, public and private. Whether this evidence rises to the level of a traditionally defined 'fact' is not necessarily the right question. Very little traditionally produced biomedical research ever becomes unequivocal fact because what is true for one set of experimental conditions may be different for other conditions…The narrower the scope of diets being investigated, the more compromised becomes the evidence supporting food guidelines for the larger population."

"Among diet and health studies on large cohorts of people, virtually none of these cohorts, to date, have included individuals accustomed to using the whole food plant-based dietary lifestyle. Vegans and vegetarians approach the nutrition of this dietary lifestyle and, in doing so, are known to have lower mortality rates for non-communicable chronic diseases [Sobiecki JG, Nutr Res 2016; 36:464-77][Huang T, Ann Nutr Metab 2012; 60:233-40], but this cannot be the full expression of health effects because, according to the most robust dietary studies on vegans and vegetarians, the mean contents of total fat and sugar for vegans, vegetarians and meat eaters were the same, 30-31% fat and 22-23% sugar" [Sobiecki JG, Nutr Res 2016; 36:464-77]."

"There is still an abundance of evidence which supports, as a goal, the use of a diet wholly composed of whole food plant-based foods, without added oil or refined carbohydrates. Two kinds of evidence convincingly expose the need for dietary change and offer a solution to support this change. These are 1) breadth of effect [Campbell TMI, Primary Care Reports 2012; 18:25-35], and 2) reversal of disease [Esselstyn CB Jr, J Fam Pract 1995; 41:560-8 and Am J Cardiol 1999; 84:339-41][Ornish D, Lancet 1990; 336:129-33]. Breadth of effect evidence challenges the contemporary and popular concept of 'targeted drug therapy,' which encourages research and development of specific drugs for controlling specific diseases…Reversal of disease means using the same nutritional protocol to prevent and to treat disease, which challenges the use of pills and procedures to control disease. Both of these kinds of evidence are best appreciated when considering and appreciating the infinitely complex, dynamic and unknowable details of nutritional function."