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Title: Plant-based diets and cardiovascular health

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Plant-based diets and cardiovascular health

Abstract

Plant-based diets, defined in terms of low frequency of animal food consumption, have been increasingly recommended for their health benefits. Numerous studies have found plant-based diets, especially when rich in high quality plant foods such as whole grains, fruits, vegetables, and nuts, to be associated with lower risk of cardiovascular outcomes and intermediate risk factors. This review summarizes the current evidence base examining the associations of plant-based diets with cardiovascular endpoints, and discusses the potential biological mechanisms underlying their health effects, practical recommendations and applications of this research, and directions for future research. Healthful plant-based diets should be recommended as an environmentally sustainable dietary option for improved cardiovascular health.

The potentially beneficial role of plant-based diets in cardiovascular health has been increasingly recognized, with a vast and accumulating evidence-base documenting their health effects (1, 2). Complementary findings from studies of individual plant and animal foods as well as their constituent nutrients lend further support to the potential cardio-protective effects of plant-based diets. Most recently, based on a comprehensive review of these studies, the Dietary Guidelines for Americans 2015-2020 (3) included a healthy vegetarian-style dietary pattern in its recommendations of dietary patterns that can be adopted for improved health. In the present review, we will provide an overview of the cardiovascular benefits associated with plant-based diets, while discussing the biological pathways potentially involved, as well as clinical applications and public health implications of these findings.

Definition of plant-based diets

Plant-based diets consist of a diverse family of dietary patterns, defined in terms of low frequency of consumption of animal foods (4). Vegetarian diets are a subset of plant-based diets which exclude intake some or all animal foods entirely. On the extreme end, vegan diets exclude consumption of all animal products. Lacto-vegetarians consume dairy products but no other animal foods, and lacto-ovo-vegetarians consume eggs and dairy products while excluding other animal foods. Pesco-vegetarians or pescetarians consume fish in addition to eggs and dairy, but exclude poultry and red meat from their diet. Some studies have also examined semi-vegetarian diets, which are sometimes defined in terms of exclusion of just red meat (4), and at others times as infrequent intake of poultry and red meat (5).

Instead of defining plant-based diets in terms of the complete exclusion of some or all animal foods as is the case with studies of vegetarianism, a few recent investigations have examined gradations of adherence to a predominantly plant-based diet. The first of these, the pro-vegetarian diet score, was defined by Martinez-Gonzalez et al. (6) as a diet which positively

67 weighs plant foods while negatively weighing animal foods. They conceptualized such a diet as
68 “a progressive and gentle approach to vegetarianism… that incorporates a range of
69 progressively increasing proportions of plant-derived foods and concomitant reductions in
70 animal-derived foods” (6)[p2S]. The advantage of such a definition is its wider applicability, as
71 recommendations of moderate dietary changes, such as gradual reductions in animal food
72 intake may be easier to adopt and adhere to than more extreme recommendations, such as
73 complete exclusion of animal foods.
74
75 Plant-based diets are usually defined in terms of the proportion and frequency animal foods
76 consumed in the diet, with little consideration given to the types and frequencies of plant foods
77 consumed. However, not all plant foods are the same, and a wide diversity of plant-based diets
78 exists based on the quality of plant foods included in the diet, each with potentially distinct
79 cardio-metabolic effects. We examined two such variations of graded plant-based diets: a
80 healthful plant-based index which positively weighs healthy plant foods (e.g. whole grains, fruits,
81 vegetables, nuts, legumes) (7-10) and negatively weighs less healthy plant foods (e.g. refined
82 grains, potatoes, sugar-sweetened beverages [SSBs]) (11-15) and animal foods; and an
83 unhealthful plant-based diet index, which positively weighs less healthy plant foods and
84 negatively weighs healthy plant foods and animal foods. We found varying cardio-metabolic
85 effects of these diet indices (16, 17), pointing to the importance of defining plant-based diets in
86 terms of the quality of plant foods they emphasize.
87
88 **Associations with cardiovascular endpoints and intermediate risk factors**
89 Despite the wide variation in the definitions of plant-based diets in the literature, their
90 associations with cardiovascular endpoints in prospective cohort studies have been fairly
91 consistent. Most studies of vegetarian diets have been carried out in Europe, with one study in
92 Japan, and three studies among Seventh Day Adventists in the US. In a pooled analysis of 5 of

the above cohorts, Key et al. (18) found a 24% (95% Confidence Interval [CI]: 6%-38%) lower rate of coronary heart disease (CHD) mortality among vegetarians relative to omnivores, although they didn't find any association with stroke mortality; two recent meta-analyses which included more studies found similar results (Figure 1) (19, 20). In many of these studies, the inverse associations were stronger among younger participants, among participants with a longer duration of adherence to a vegetarian diet, and among men relative to women. In particular, the most recent meta-analysis found a 22% (95% CI: 12%-31%) lower rate of stroke mortality among vegetarian men relative to their omnivore counterparts, but the association was not significant among women (20).

Studies of graded plant-based diet indices have also found similar results. Comparing the highest with the lowest category of adherence, Martinez-Gonzalez et al. (6) found a pro-vegetarian diet score to be associated with a lower rate of cardiovascular mortality (Hazard Ratio [HR]: 0.47; 95% CI: 0.21 to 1.04; p-trend=0.039) over a median follow-up of 5 years in the PREDIMED trial in Spain. Over a longer duration of follow-up (median=12.8 years) in a large European cohort, Lassale et al. (21) found a 20% (95% CI: 7%-30%) lower cardiovascular death rate comparing extreme categories. Recently, we conducted a similar analysis in more than 200,000 male and female health professionals in the Nurses Health Studies and the Health Professionals Follow-up Study in the US (Figure 2) (17). An overall plant-based diet index (similar to the pro-vegetarian diet score) was modestly inversely associated with incident CHD (HR comparing extreme deciles: 0.92; 95% CI: 0.83 to 1.01; p-trend=0.003). This inverse association was substantially stronger for a healthful version of this graded plant-based diet index (HR comparing extreme deciles: 0.75; 95% CI: 0.68 to 0.83; p-trend<0.001). However, the association was positive for an unhealthful version of the index (HR comparing extreme deciles: 1.32; 95% CI: 1.20 to 1.46; p-trend<0.001).

Given the likely long induction periods of cardiovascular diseases, especially with respect to their dietary etiology, plant-based diets have not been examined in randomized controlled trials (RCTs) of hard cardiovascular endpoints. Nevertheless, several RCTs have examined the effect of vegetarian diets on intermediate risk factors of cardiovascular diseases (Table 1). In a meta-analysis of RCTs, Wang et al. (22) found vegetarian diets to significantly lower blood concentrations of total, LDL, HDL, and non-HDL cholesterol relative to a range of omnivorous control diets. Other meta-analyses have found vegetarian diets to lower blood pressure, enhance weight loss, and improve glycemic control to greater extent than omnivorous comparison diets (23-25). Taken together, the beneficial effects of such diets on established proximal determinants of cardiovascular diseases found in RCTs, and their inverse associations with hard cardiovascular endpoints found in prospective cohort studies provide strong support for the adoption of healthful plant-based diets for cardiovascular disease prevention.

Potential biological mechanisms

A healthful plant-based diet, which emphasizes intake of whole grains, fruits, vegetables, nuts and legumes, tea and coffee, and non-hydrogenated vegetable oils, might affect cardiovascular health through numerous potential biological pathways (Figure 3). Such a diet is likely to be low in energy density due to its low saturated fat and high fiber content, which could help with weight loss and long-term weight maintenance. In particular, dietary fiber might lower energy intake by triggering satiety cues such as increased gastric distention, likely caused by the augmented chewing of fibrous foods, together with gel formation due to water absorption by soluble fiber (26). The viscous gel formation by soluble fiber may also delay gastric emptying and prolong nutrient absorption, further promoting satiety and moderating post-prandial insulinemic and glycemic responses (26). Another key mechanism through which dietary fiber may improve cardiovascular health is through its potential cholesterol lowering effect. In a meta-analysis of RCTs, a 2-10 g/day increase in soluble fiber intake resulted in a modest but

145 significant -0.057 mmol/L decrease in LDL cholesterol (95% CI: -0.070, -0.044 mmol/L) (27),
146 probably mediated by lower cholesterol and fat absorption, altered cholesterol synthesis,
147 increased bile acid synthesis, and decreased bile acid absorption (28).
148
149 The low saturated fat and high unsaturated fat contents of a healthful plant-based diet may
150 lower CVD risk by improving the blood lipid profile. In meta-analyses of RCTs, replacing
151 saturated fatty acids with polyunsaturated fatty acids lowered total:HDL cholesterol ratio (29), as
152 well as CHD risk (30) in a dose response manner, with similar results observed in prospective
153 cohort studies (31). In vitro studies have shown saturated fatty acids to activate the pro-
154 inflammatory TLR4 signaling pathway (32). Saturated fatty acids may also interact with the gut
155 microbiome to promote the translocation of lipopolysaccharide (LPS), a potent pro-inflammatory
156 endotoxin, into the bloodstream (33). On the other hand, there is some evidence that
157 polyunsaturated fatty acids activate anti-inflammatory pathways (34, 35). Thus, a high
158 unsaturated fat and low saturated fat diet may also lower CVD risk through its potential anti-
159 inflammatory effects. Replacing saturated fats with polyunsaturated and monounsaturated fats
160 may also enhance insulin sensitivity and prevent type 2 diabetes, possibly through altering cell
161 membrane fatty acid composition and hence cell membrane function, moderating gene
162 expression and enzyme activity, and mediating the inflammatory response (32).
163
164 Plant foods such as whole grains, fruits, vegetables, vegetable oils, nuts, tea, coffee, and cocoa
165 are also rich in polyphenols, natural bioactive compounds produced by plants as secondary
166 metabolites essential for plant physiology (36). The numerous individual polyphenols are
167 classified into four major classes based on structure, which account for most of the polyphenols
168 found in human diet: flavonoids, lignans, phenolic acids, and stilbenes (37). The antioxidant
169 capacity of such polyphenol compounds, largely through their role in scavenging and
170 neutralizing free oxygen and nitrogen species and protecting against oxidative stress is known

171 from in vitro studies (37). This antioxidant capacity, potentially together with their ability to
172 modulate nitric oxide (NO) production, enables polyphenol compounds to help maintain vascular
173 homeostasis (38). Polyphenols might also contribute to improved cardiovascular health through
174 their roles in inhibiting platelet aggregation, reducing vascular inflammation, modulating
175 apoptotic processes, limiting LDL oxidation, and improving lipid profile (38, 39). A healthful
176 plant-based diet is also replete with numerous other antioxidant nutrients such as vitamins C
177 and E and beta-carotene; potassium which has been shown to reduce blood pressure and lower
178 stroke risk through its beneficial effects on endothelial function and vascular homeostasis (40,
179 41); and magnesium which has been associated with improved cardio-metabolic outcomes due
180 to its effects on glucose metabolism and insulin sensitivity, and its anti-inflammatory,
181 vasodilatory, and antiarrhythmic properties (42, 43).
182
183 On the other hand, several dietary factors that are abundant in animal foods have been
184 associated with increased risk of cardiovascular endpoints. For instance, heme iron, found
185 mainly in animal foods such as red meat, poultry, and seafood, has been associated with higher
186 risk of cardiovascular endpoints in several prospective cohort studies (44-48). It is postulated
187 that the oxidative potential of iron resulting in the production of reactive oxygen species and
188 oxidative stress, couple with the higher absorption and bioavailability of heme iron could
189 mediate this association (45). Other nutrients used to preserve processed meats, such as
190 sodium, nitrates, and nitrites may also increase risk of cardiovascular outcomes through raised
191 blood pressure, impaired insulin response, and endothelial dysfunction (49).
192
193 The gut microbiome represents another novel pathway through which a healthful plant-based
194 diet may influence cardiovascular risk. The complex community of microorganisms that reside in
195 the human gut metabolizes otherwise undigestible dietary substrates to potentially influence the
196 cardiovascular health of the human host (50, 51). An example of this is the trimethylamine N-

oxide (TMAO) pathway. Choline and L-carnitine, compounds derived mainly from animal foods such as red meat, poultry, and fish are broken down by gut microbes to generate trimethylamine (TMA), which is further broken down to TMAO in the liver (52). TMAO has been associated with a higher risk of cardiovascular events independent of traditional risk factors, and it is postulated that it influences cardiac health through its effects on cholesterol and sterol metabolism, inflammation, and thrombotic and atherosclerotic pathways (53). Given that a recent study found no correlation between TMAO and dietary factors (54), it is possible that associations of animal foods with cardiac risk through the TMAO pathway are modified by level of dietary intake of foods rich in TMAO precursors, as well as by gut microbial composition. Plant foods are also rich in certain TMAO precursors such as betaine. However, in animal models, certain plant compounds (e.g. resveratrol) have been found to potentially inhibit TMAO production (55, 56). Plant-based diets differ from animal-based diets with respect to many other microbe-dependent metabolic pathways as well, including increased metabolism of fiber and polyphenols, and decreased metabolism of bile acids and amino acids (57-59), which could mediate their inverse associations with cardiovascular endpoints. Larger studies with longer follow-up and repeat assessments of diet, the metabolome, and the microbiome are needed to clarify the likely complicated pathways through which diet interacts with the gut microbial environment to impact cardiovascular health.

Conclusions

Plant-based diets, defined in terms of varying degrees of restrictions on animal food consumption, have been associated with lower risk of cardiovascular diseases as well as an improved cardiovascular risk profile. In addition, numerous biological mechanisms exist through which healthful plant foods may exert their potentially cardio-protective effects. However, there has been some concern about the nutritional adequacy of vegetarian diets, especially vegan diets which completely exclude all animal foods. While the bioavailability of certain nutrients

such as iron, zinc, and vitamin A (obtained from conversion of carotenoids) is lower in plant than animal foods, these nutrients can be obtained in the recommended amounts in well planned vegan diets which include a wide variety of healthful plant foods (60). Other nutrients such as vitamins B12 and D are mostly found in animal foods; however, use of supplements, consumption of fortified foods, and in the case of vitamin D, sunlight exposure can ensure adequate levels in vegans (60). The Academy of Nutrition and Dietetics (60), the American Heart Association (61), and the 2015-2020 Dietary Guidelines for Americans (3) recommend appropriately planned vegetarian diets for improved health.

The consistent beneficial associations observed with a wide variation of plant-based diets also allows for personalized and culturally relevant applications of dietary recommendations. For individuals who prefer not to consume certain or most animal foods, healthful and well-planned plant-based meals can provide adequate nutrition and cardiovascular benefits. For those who prefer a more moderate approach, health benefits may be observed even with gradual reductions in animal food intake when replaced with healthy plant foods. For all types of plant-based diets however, it is crucial that the choice of plant foods is given careful consideration. Individuals should choose whole grains over refined grains, whole fruits over fruit juices, unrefined vegetable oils over partially hydrogenated versions, and healthful and unsweetened beverages such as water, tea, and coffee over sweetened beverages, while reducing potatoes/French fries and foods with added sugar. A wider adoption of healthful plant-based diets and a decrease in intake of animal foods, in particular red meat, would also have favorable environmental impacts, as production of plant foods requires fewer natural resources with lower greenhouse gas emissions than that of animal foods (62-64).

In conclusion, considerable evidence supports the cardiovascular benefits of healthful plant-based diets, and these diets and their constituent foods are getting increasing recognition in

249 dietary recommendations. Future research should examine policy strategies to translate the
250 findings of these studies to the wider population, and further explore mechanistic pathways
251 through which healthful plant-based diets may improve cardiovascular health.
252

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Table 1: Summary effect estimates of meta-analyses of RCTs examining the effects vegetarian diets on cardiovascular risk factors

Author (year)	Endpoint	Types of control diets	Summary effect estimate comparing vegetarian with control diets
Wang (2015) (22)	Total cholesterol LDL cholesterol HDL cholesterol Triglycerides Non-HDL cholesterol	Usual diet, ADA diet, Prudent diet with lean meat, Low fat diet, Diabetic diet	-0.36 mmol/L (-0.55, -0.17)* -0.34 mmol/L (-0.57, -0.11)* -0.10 mmol/L (-0.14, -0.06)* 0.04 mmol/L (-0.05, 0.13) -0.30 mmol/L (-0.50, -0.10)*
Yokoyama (2014) (23)	Systolic blood pressure† Diastolic blood pressure†	Usual diet, Prudent diet with lean meat, Low fat diet	-4.8 mmHg (-6.6, -3.1)* -2.2 mmHg (-3.5, -1.0)*
Huang (2015) (24)	Body weight	Usual diet, Diabetic diet, Low fat diet, NCEP diet, Low carb diet, High carb diet, High protein (from meat) diet	-2.02 kg (-2.80, -1.23)*
Yokoyama (2014) (25)	HbA1c†† Fasting blood glucose	Usual diet, ADA diet, Low fat diet, Diabetic diet	-0.39% (-0.62, -0.15)* -0.36 mmol/L (-1.04, 0.32)

RCT, Randomized Controlled Trial; LDL, Low-Density Lipoprotein; HDL, High-density lipoprotein; HbA1c, glycated hemoglobin; ADA, American Diabetes Association; NCEP, National Cholesterol Education Program

** P value<0.05*

† 1 trial out of 7 trials was non-randomized

†† 2 trials out of 5 trials were non-randomized

Figure 1: Summary effect estimates (95% CI) of pooled and meta-analyses of vegetarian diets in relation to CHD or stroke mortality(18-20)

CHD, Coronary Heart Disease; CI, Confidence Interval; RR, Relative Risk

Figure 2: Dose-response relationship of plant-based diet indices with CHD incidence(17)

CHD, Coronary Heart Disease; HR, Hazard Ratio; PDI, Overall Plant-based Diet Index; hPDI, Healthful Plant-based Diet Index; uPDI, Unhealthful Plant-based Diet Index

For uPDI, p for test of curvature = 0.01 and p for nonlinear association <0.001. The p values for test of curvature for PDI = 0.25, and for hPDI = 0.82. The p values for linearity = 0.001 for PDI, and <0.001 for hPDI.

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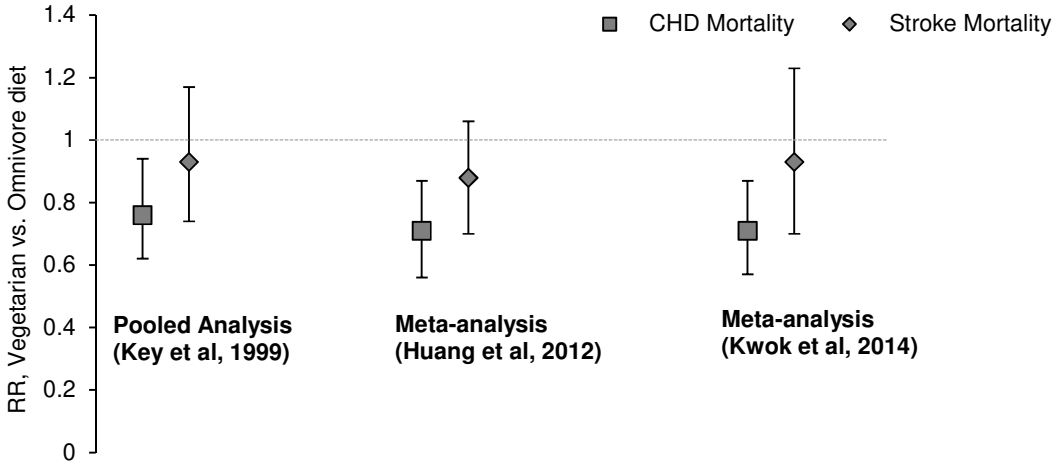
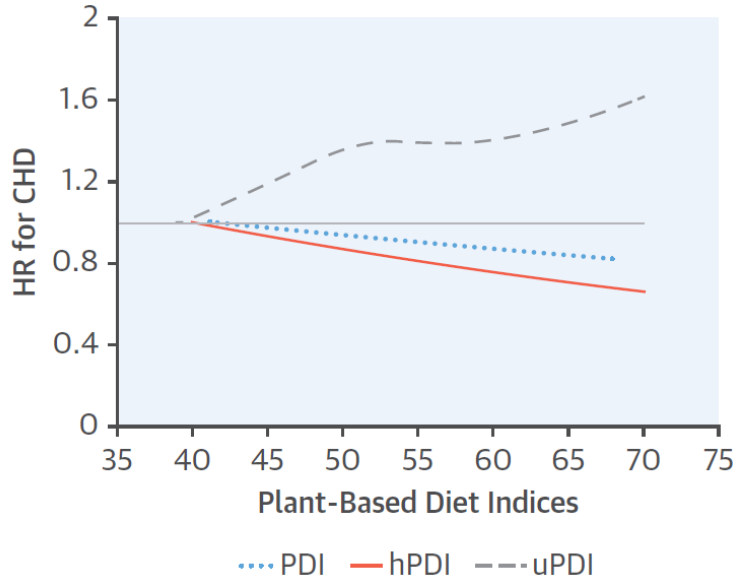
Figure 3: Potential mechanisms underlying the cardiovascular effects of healthful plant-based diets

Figure 1: Summary effect estimates (95% CI) of pooled and meta-analyses of vegetarian diets in relation to CHD or stroke mortality[7-9]



CHD, Coronary Heart Disease; CI, Confidence Interval; RR, Relative Risk

Figure 2: Dose-response relationship of plant-based diet indices with CHD incidence[6]



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