After decades of epidemiological and clinical research, the influence of overall diet on health and disease, particularly coronary heart disease (CHD), has become widely accepted. The pioneering ecological and metabolic studies of Keys and colleagues placed the focus on fat types, showing that populations consuming more saturated fatty acids (SFAs) had higher blood cholesterol levels and associated higher rates of CHD, whereas individuals fed SFAs had increased blood cholesterol levels, as opposed to the effects of monounsaturated or polyunsaturated fatty acids (PUFAs). Cholesterol changes derived from switching fatty acid species in the diet were found to be predictable with specific equations. Subsequent epidemiological studies confirmed that elevated serum cholesterol was a strong independent risk factor for CHD. This led to the formulation of the diet-heart hypothesis, whereby the high intake of saturated fats leads to elevated cholesterol levels, which in turn promote atherosclerosis, coronary artery occlusion, and subsequent ischemic events. Although the diet-heart hypothesis shaped dietary guidelines toward reduction of all dietary fat, with a concomitant increase in carbohydrates, a low-fat approach was not effective in reducing the incidence of cardiovascular disease (CVD) in women. In the past 3 decades, the decreasing fat consumption as a percentage of energy in the US population has done little to slow the increasing rates of obesity and type 2 diabetes mellitus (T2DM). It is now widely recognized that higher-fat diets can be beneficial if healthy fats are consumed, whereas high-carbohydrate diets (particularly those with high glycemic load) might be contributing to CHD and other negative health outcomes. As reviewed here, healthy, plant-based unsaturated fats are major components of widely consumed edible seeds, such as tree nuts and peanuts.

More important than isolated foods or nutrients, the effect of overall dietary patterns on disease risk has become a new approach in nutritional epidemiology. Plant-based dietary patterns, such as the prudent diet identified by Hu et al contain high amounts of vegetables, legumes, whole grains, and fruit and moderate amounts of fish, poultry, and low-fat dairy products. This dietary pattern has been associated with lower risk of CVD and T2DM and is widely recommended for heart health. The traditional Mediterranean diet, which is akin to the prudent diet but has a higher total fat content in the form of olive oil and also alcohol (red wine) in moderation, has emerged as another dietary approach to chronic disease prevention, including CVD. Another potentially healthy dietary pattern is the so-called Paleolithic diet, still consumed by hunter-gatherer societies worldwide and put into perspective by Eaton and Conner >25 years ago. The hunter-gatherer’s diet is high in slow-release carbohydrate and fiber from plant foods, high in protein from lean wild animal meat and plant seeds, and low in fat, which is mostly unsaturated and derived from both wild game meat and seed sources, with contributions to total energy intake of ≈45%, 35%, and 20%, respectively. Noticeably, of the plant foods foraged by hunter-gatherers, an average 41% is made up of fruit and 26% comes from nuts and whole seeds, considerably higher than amounts consumed by modern humans, including former hunters-gatherers settled into a Westernized existence.

The integral role of seeds in preagricultural diets is understandable given their high energy and nutrient density. Seeds are also particularly important in human nutrition because of their unique composition in bioactive compounds. Of note, in the past decade, a large body of scientific evidence has been built on the beneficial effects of increasing the consumption of plant seeds and derived products on various health outcomes, chiefly CVD, T2DM, and intermediate markers. The purpose of this review is to summarize the state of the evidence for the cardiovascular health effects of plant seeds, a food category bound to have a prominent place in health-promoting diets.

Data Sources and Selection of Studies on Plant Seeds and Cardiovascular Health

For this narrative review we conducted a comprehensive search of MEDLINE and EMBASE through December 2012 for English language descriptions of seed composition, reports of epidemiological and clinical studies describing the effects of seeds (whole grains, tree nuts and peanuts, pulses, cocoa and cocoa products such as chocolate, and coffee) on cardiometabolic outcomes, and the most recent reviews and meta-analyses of these studies. We also searched for reviews

From the Lipid Clinic, Endocrinology & Nutrition Service, Institut d’Investigacions Biomèdiques August Pi Sunyer, Hospital Clinic, Barcelona and CIBER Fisiopatología de la Obesidad y Nutrición (CIBERobn), Instituto de Salud Carlos III (ISCIII), Spain (E.R.); and Departments of Nutrition and Epidemiology, Harvard School of Public Health, Boston, MA (F.B.H.).

Drs Ros and Hu contributed equally to this work.

Correspondence to Emilio Ros, MD, PhD, Lipid Clinic, Endocrinology & Nutrition Service, Hospital Clinic, C. Villarroel, 170, 08036 Barcelona, Spain. E-mail eros@clinic.ub.es and Frank B. Hu, MD, PhD, Department of Nutrition, Harvard School of Public Health, 665 Huntington Ave, Boston, MA 02115. E-mail frank.hu@channing.harvard.edu

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and meta-analyses of the effects of the main bioactive seed components on the same outcomes. Finally, we searched references cited in original studies and reviews identified, together with articles citing landmark clinical studies, reviews, and meta-analyses, as provided by the publishers of individual articles in their Websites. Data were examined for relevance, quality, and consistency and independently extracted by the 2 authors, who reached a consensus when in doubt about a specific citation. Given that, up to the time of submission, few controlled trials on the effects of seed consumption on clinical end points had been published, we have derived the core of scientific evidence from prospective cohort studies reporting disease outcomes and RCTs with intermediate end points, with a particular emphasis on meta-analyses of such studies.

Broad Definition of Seeds and Their Purpose in Nature

Seeds are small embryonic plants enclosed in a coat, the product of the ripened ovule of flowering plants after pollination and the completion of the process of reproduction. Seeds are made of complex matrices in the outer layer and the germ, rich in minerals, vitamins, and bioactive phytochemicals that protect the plant’s DNA from oxidative stress, thus facilitating the perpetuation of the species.28 On the other hand, the endosperm of seeds stores nutritive components to sustain the future seedling with a variable mixture of high-quality protein, complex carbohydrate, and fat depending on the type of seed. In this sense, seeds are like eggs, which also contain nutrients to sustain the growth of bird and reptile embryos. For instance, seeds contain sizable amounts of phytosterols, important structural components of plant membranes that stabilize phospholipid bilayers just as the cholesterol that abounds in eggs does in animal cell membranes.29 Whole seeds provide a wide array of bioactive molecules likely to have significant health benefits.

Widely Consumed Seeds

Edible seeds having a significant contribution to human nutrition include grains (cereals), nuts, legumes, and cocoa and coffee beans. Human populations derive most of their energy needs from seeds or seed products, particularly grains (wheat, corn, and rice) and legumes (soybeans). Seeds also provide most dietary oils and widely consumed beverages (coffee).

Grains (cereals) include wheat, oats, rye, rice, barley, millet, and corn.30 The foods originating from them range from highly nutrient-dense whole grain breads and cereal foods such as oats, to less nutrient-dense white rice, white bread, pasta and noodles or refined grain products with high levels of added sugar, fat, and sodium, such as many biscuits, pastries, and cakes.

Nuts are dry fruits with 1 seed in which the ovary wall becomes hard at maturity. The most popular edible tree nuts are almonds, walnuts, hazelnuts, and pistachios. Other common edible nuts are pine nuts, cashews, pecans, macadamias, and Brazil nuts.31 The consumer definition also includes peanuts, which botanically are legumes but are widely identified as part of the nuts food group. In addition, peanuts have a similar nutrient profile to tree nuts.32

Pulses are the seeds of leguminous plants contained within pods. Lentils, chickpeas, black-eyed peas, and a variety of dry beans, including pinto, kidney, navy, and fava beans, are the most common edible pulses.33 The term pulses excludes legumes used for oil extraction, such as soybeans and peanuts, and those harvested green, such as green peas and green beans, which are classified as vegetables. Pulses usually require cooking before consumption and are eaten untransformed, unlike soybeans, which are the basis for soy oil and various foods such as tofu and derived products, widely consumed in Asia and by vegetarian populations worldwide.

Cocoa beans are the seeds of the tropical tree Theobroma cacao. The main product derived from cocoa is chocolate, a variable combination of cocoa solids, cocoa butter, milk, and sugar.34 The roasted, ground seeds of the Coffea plant are used to brew coffee, which competes with tea as the most consumed beverage worldwide.

Grains, nuts, legumes, and cocoa products represent a sizable contribution to human energy consumption in various populations, whereas daily coffee drinking is customary for many individuals worldwide. Many other edible seeds that are sparingly consumed and contribute only marginally to energy intake will not be dealt with here: pepper, mustard, cumin, capers and other seasoning seeds; flax, hemp, pumpkin, sesame, and sunflower seeds; berries; and others like coconut.

Composition of Edible Seeds

The macro- and micronutrients, minerals, vitamins, and phytochemicals in seeds reflect their role of nourishment and protection of the future seedling (Table 1 and Table 2). Edible seeds, particularly fat-rich nuts and cocoa products, are good sources of energy (Table 1). Brewed coffee is an exception because of the lack of macronutrients. The protein from seeds provides most essential amino acids, although some foods must be complemented to obtain significant amounts of all of them. For instance, the content of sulfur amino acids methionine and cysteine is marginal in most nuts38 and pulses,39 whereas grains contain sizable quantities,40 a reason why mixing the former with cereals suffices to meet human requirements. Again, with the exception of coffee, seeds are rich in carbohydrate and fiber (Table 1). Most energy in nuts comes from fat, but fatty acids are mostly unsaturated. Some nuts, especially walnuts, contain sizable amounts of PUFA, including linoleic acid (18:2n-6) and α-linolenic acid (C18:3n-3), the principal plant n-3 fatty acid.42 Conversely, SFAs abound in cocoa seeds, but the predominant species is stearic acid (C18:0), the consumption of which does not raise cholesterol as shorter-chain SFAs do.40

Regarding micronutrients (Table 2), the folate content of seeds and seed products ranges from low to moderate, but frequent consumption is likely to contribute to adequate folate intake. The seed content of tocopherols (the main vitamin E compounds) is also low to moderate, with the exception of nuts, which can be particularly rich in α-tocopherol, the principal vitamin E species. Regarding minerals, seeds are excellent sources of potassium (K⁺), magnesium (Mg²⁺) (excluding coffee), and calcium (Ca²⁺). Like all vegetables, unprocessed seeds have very low sodium content. Seeds contain enough phytosterols to build the cell membranes of the future
Table 1. Average Nutrient Composition of Selected Seeds and Seed Products

<table>
<thead>
<tr>
<th>Seeds</th>
<th>Energy, kJ</th>
<th>Protein, g</th>
<th>Carbohydrate, g</th>
<th>Fiber, g</th>
<th>Total Fat, g</th>
<th>SFA, g</th>
<th>MUFA, g</th>
<th>PUFA, g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole grain flour</td>
<td>465–1587</td>
<td>2.6–15.9</td>
<td>23.0–76.9</td>
<td>1.8–23.8</td>
<td>0.9–6.5</td>
<td>0.2–1.1</td>
<td>0.2–2</td>
<td>0.3–2.6</td>
</tr>
<tr>
<td>Tree nuts and peanuts</td>
<td>2200–3000</td>
<td>7.8–23.7</td>
<td>12.3–32.7</td>
<td>3.0–12.2</td>
<td>46.0–76.1</td>
<td>3.7–11.9</td>
<td>8.9–59.3</td>
<td>1.5–47.2</td>
</tr>
<tr>
<td>Pulses (baked)</td>
<td>352–687</td>
<td>4.8–9.0</td>
<td>15.6–27.4</td>
<td>5.4–10.5</td>
<td>0.2–2.6</td>
<td>0.04–0.27</td>
<td>0.02–0.58</td>
<td>0.1–1.2</td>
</tr>
<tr>
<td>Dark chocolate</td>
<td>2286–2504</td>
<td>4.9–7.8</td>
<td>45.9–61.2</td>
<td>7.0–10.9</td>
<td>31.3–42.6</td>
<td>18.5–24.5</td>
<td>9.5–12.8</td>
<td>1.1–1.3</td>
</tr>
<tr>
<td>Coffee (per cup)*</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.05</td>
<td>0.005</td>
<td>0.036</td>
</tr>
</tbody>
</table>

Data for raw products and 100-g serving size, except where specified. MUFA indicates monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; and SFA, saturated fatty acids.

*One cup is made from ≈5 g of ground coffee.

Data derived from US Department of Agriculture Nutrient Database and other databases.

Table 2. Average Composition of Seeds and Seed Products in Selected Micronutrients, Minerals, and Phytochemicals

<table>
<thead>
<tr>
<th>Seeds</th>
<th>Folate, μg</th>
<th>Tocopherols, mg</th>
<th>Potassium, mg</th>
<th>Calcium, mg</th>
<th>Magnesium, mg</th>
<th>Phytosterols, mg</th>
<th>Polyphenols, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole grain flour</td>
<td>4–44</td>
<td>0.03–2.7</td>
<td>43–717</td>
<td>7–52</td>
<td>43–160</td>
<td>28–89</td>
<td>72–95</td>
</tr>
<tr>
<td>Tree nuts and peanuts</td>
<td>10–145</td>
<td>0.9–26.2</td>
<td>363–1042</td>
<td>16–264</td>
<td>118–1223</td>
<td>72–214</td>
<td>126–1816</td>
</tr>
<tr>
<td>Pulses (baked)</td>
<td>47–208</td>
<td>0.01–0.94</td>
<td>194–508</td>
<td>19–69</td>
<td>36–70</td>
<td>108–121</td>
<td>120–6500</td>
</tr>
<tr>
<td>Dark chocolate*</td>
<td>7–10</td>
<td>0.54–0.59</td>
<td>559–715</td>
<td>56–73</td>
<td>146–228</td>
<td>102–129</td>
<td>1105–1860</td>
</tr>
<tr>
<td>Coffee (per cup)†</td>
<td>5</td>
<td>0.04</td>
<td>116</td>
<td>5</td>
<td>7</td>
<td>0.2</td>
<td>267</td>
</tr>
</tbody>
</table>

Data for raw products and 100-g serving size, except where specified. Polyphenol data for pulses correspond to raw products.

*45% to 85% cacao solids.
†One cup is made from ≈5 g ground coffee.

Data derived from US Department of Agriculture Nutrient Database, National Institute for Health and Welfare, N.U. Finelli, Finnish Food Composition Database, Phenol-Explorer 2.0 Database on polyphenol content in foods.
<table>
<thead>
<tr>
<th>Author (Year), Reference</th>
<th>Type of Study</th>
<th>n</th>
<th>Population</th>
<th>Follow-Up</th>
<th>Outcomes</th>
<th>Effect of Increased Seed Consumption*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ye (2012)45</td>
<td>Meta-analysis of 8 cohort studies</td>
<td>298,592</td>
<td>Generally healthy</td>
<td>6–14 y</td>
<td>Incident CVD</td>
<td>RR=0.79 (0.74–0.85)</td>
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<tr>
<td></td>
<td>Meta-analysis of 6 cohort studies</td>
<td>288,319</td>
<td>Generally healthy</td>
<td>6–12 y</td>
<td>Incident T2DM</td>
<td>RR=0.74 (0.69–0.80)</td>
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<tr>
<td></td>
<td>Meta-analysis of 21 RCTs</td>
<td>Not available</td>
<td>Healthy or patients with HC or hypertension</td>
<td>4–16 wk</td>
<td>Lipid profile</td>
<td>Δ Total cholesterol: −0.83 mmol/L (−1.24 to −0.42)</td>
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<td></td>
<td>Δ LDL-cholesterol: −0.27 mmol/L (−1.34 to −0.11)</td>
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<td></td>
<td>Glycemic control</td>
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<tr>
<td>de Munter (2007)46</td>
<td>Meta-analysis of 6 cohort studies</td>
<td>286,125</td>
<td>Generally healthy populations</td>
<td>6–18 y</td>
<td>Incident T2DM</td>
<td>21% (13%–28%) risk reduction for a 2-servings per day increment</td>
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<tr>
<td>Kris-Etherton (2008)47</td>
<td>Pooled analysis of 4 US prospective studies</td>
<td>135,604</td>
<td>CVD-free men and women</td>
<td>6–17 y</td>
<td>Incident CHD</td>
<td>RR=0.65 (0.47–0.89)</td>
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<tr>
<td>Banel and Hu (2009)48</td>
<td>Meta-analysis of 13 walnut RCTs</td>
<td>365</td>
<td>Subjects with normal lipids or HC</td>
<td>4–24 wk</td>
<td>Lipid profile</td>
<td>Δ Total cholesterol: −0.27 mmol/L (−0.38 to −0.15)</td>
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<td>Δ LDL-cholesterol: −0.24 mmol/L (−0.34 to −0.14)</td>
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<tr>
<td>Sabaté (2010)49</td>
<td>Pooled analysis of 27 nut RCTs</td>
<td>583</td>
<td>Subjects with normal lipids or HC</td>
<td>3–8 wk</td>
<td>Lipid profile</td>
<td>Δ Total cholesterol: −0.28 mmol/L (−0.37 to −0.20)</td>
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<td>Δ LDL-cholesterol: −0.26 mmol/L (−0.34 to −0.19)</td>
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<tr>
<td>Pulses</td>
<td>Bazzano (2011)50</td>
<td>Meta-analysis of 10 RCTs</td>
<td>268</td>
<td>Subjects with normal lipids or HC</td>
<td>3–8 wk</td>
<td>Lipid profile</td>
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<td>Δ LDL-cholesterol: −0.21 mmol/L (−0.30 to −0.12)</td>
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<td>Δ Triglycerides: −1.67 mmol/L (−3.63 to 0)</td>
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<tr>
<td>Sievenpiper (2009)51</td>
<td>Meta-analysis of 11 RCTs of pulses alone</td>
<td>253</td>
<td>Subjects with T2DM, normoglycemia or HC</td>
<td>1–96 wk</td>
<td>Glycemic control</td>
<td>(Results as SMD)†</td>
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<td>Fasting glucose: −0.82 (−1.36 to −0.27)</td>
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<td>Fasting insulin: −0.49 (−0.93 to −0.04)</td>
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<tr>
<td></td>
<td>Meta-analysis of 19 RCTs of pulses in low-GI diets</td>
<td>72</td>
<td>Subjects with type 1 diabetes mellitus, T2DM or normoglycemia</td>
<td>2–52 wk</td>
<td>HbA1c: −0.28 (−0.42 to −0.14)</td>
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<tr>
<td></td>
<td>Meta-analysis of 11 RCTs of pulses in high-fiber diets</td>
<td>641</td>
<td>Subjects with type 1 diabetes mellitus, T2DM or normoglycemia</td>
<td>1.4–156 wk</td>
<td>Fasting glucose: −0.32 (−0.49 to −0.15)</td>
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<td>HbA1c: −0.27 (−0.45 to −0.09)</td>
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<tr>
<td>Chocolate</td>
<td>Buitrago-Lopez (2011)52</td>
<td>Meta-analysis of 5 prospective studies</td>
<td>60,455</td>
<td>CVD-free men and women (patients with previous CHD in 1 study)</td>
<td>8–16 y</td>
<td>Incident CVD</td>
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</tr>
<tr>
<td>Larsson (2012)53</td>
<td>Meta-analysis of 5 prospective studies</td>
<td>131,345</td>
<td>CVD-free men and women (patients with previous CHD in 1 study)</td>
<td>8–16 y</td>
<td>Stroke</td>
<td>RR=0.71 (0.52–0.98)</td>
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<tr>
<td>Tokede (2011)54</td>
<td>Meta-analysis of 10 RCTs</td>
<td>320</td>
<td>Healthy subjects or subjects with CVD risk factors</td>
<td>2–12 wk</td>
<td>Lipid profile</td>
<td>Δ Total cholesterol: −0.16 mmol/L (−0.30 to −0.02)</td>
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<td>Δ LDL-cholesterol: −0.15 mmol/L (−0.27 to −0.03)</td>
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</table>

(Continued)
Table 3. Continued

<table>
<thead>
<tr>
<th>Author (Year), Reference</th>
<th>Type of Study</th>
<th>n</th>
<th>Population</th>
<th>Follow-Up</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hooper (2012)56</td>
<td>Meta-analysis of 21 RCTs reporting lipid outcomes</td>
<td>290</td>
<td>Healthy subjects or subjects with CVD risk factors</td>
<td>2–26 wk</td>
<td>Lipid profile $\Delta$ LDL-cholesterol: $-0.07 \text{ mmol/L}$ ($-0.14$ to $-0.0$) $\Delta$ HDL-cholesterol: $0.03 \text{ mmol/L}$ ($0.0$–$0.06$)</td>
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<td></td>
<td>Meta-analysis of 6 RCTs reporting glycemic control</td>
<td>91</td>
<td>Healthy subjects or subjects with CVD risk factors</td>
<td>2–26 wk</td>
<td>Glycemic control $\Delta$ Insulin: $-2.65 \mu\text{U/mL}$ ($-4.65$ to $-0.65$) $\Delta$ HOMA-IR: $-0.67$ ($-0.98$ to $-0.36$)</td>
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<td>Meta-analysis of 22 RCTs reporting blood pressure</td>
<td>918</td>
<td>Healthy subjects or subjects with CVD risk factors</td>
<td>2–18 wk</td>
<td>Blood pressure $\Delta$ DBP: $-1.60 \text{ mmHg}$ ($-2.77$ to $-0.43$)</td>
</tr>
<tr>
<td></td>
<td>Meta-analysis of 11 acute RCTs on postprandial FMD</td>
<td>373</td>
<td>Healthy subjects or subjects with CVD risk factors</td>
<td>90–150 min</td>
<td>FMD $\Delta$ FMD: $3.19%$ ($2.04$–$4.33$)</td>
</tr>
<tr>
<td></td>
<td>Meta-analysis of 11 chronic RCTs reporting FMD</td>
<td>382</td>
<td>Healthy subjects or subjects with CVD risk factors</td>
<td>2–18 wk</td>
<td>FMD $\Delta$ FMD: $1.34%$ ($1.00$–$1.68$)</td>
</tr>
<tr>
<td>Ried (2012)59</td>
<td>Meta-analysis of 20 RCTs</td>
<td>865</td>
<td>Healthy subjects or subjects with CVD risk factors</td>
<td>2–18 wk</td>
<td>Blood pressure $\Delta$ SBP: $-2.77 \text{ mmHg}$ ($-4.72$ to $-0.82$) $\Delta$ DBP: $-2.30 \text{ mmHg}$ ($-3.46$ to $-0.93$)</td>
</tr>
</tbody>
</table>

**Coffee**

<table>
<thead>
<tr>
<th>Author (Year), Reference</th>
<th>Type of Study</th>
<th>n</th>
<th>Population</th>
<th>Follow-Up</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wu (2009)57</td>
<td>Meta-analysis of 21 cohort studies</td>
<td>407,806</td>
<td>Generally healthy</td>
<td>4–32 y</td>
<td>Incident CHD RR=0.82 ($0.73$–$0.92$) in women RR=0.87 ($0.80$–$0.86$) in men and women followed ≤10 y</td>
</tr>
<tr>
<td>Larsson (2011)56</td>
<td>Meta-analysis of 11 cohort studies</td>
<td>479,689</td>
<td>Generally healthy</td>
<td>2–20.8 y</td>
<td>Incident stroke RR=0.86 ($0.78$–$0.94$) for 2 cups of coffee per day RR=0.83 ($0.74$–$0.92$) for 3–4 cups/d RR=0.87 ($0.77$–$0.97$) for 6 cups/d RR=0.93 ($0.79$–$1.08$) for 8 cups/d</td>
</tr>
<tr>
<td>Mostofsky (2012)56</td>
<td>Meta-analysis of 5 cohort studies</td>
<td>140,220</td>
<td>Generally healthy or patients with myocardial infarction</td>
<td>8–35 y</td>
<td>Incident congestive heart failure RR=0.90 ($0.82$–$0.99$) for 3–4 cups/d RR=0.89 ($0.81$–$0.99$) for 4–5 cups/d</td>
</tr>
<tr>
<td>Huxley (2009)59</td>
<td>Meta-analysis of 18 cohort studies</td>
<td>457,922</td>
<td>Generally healthy</td>
<td>2.6–20 y</td>
<td>Incident T2DM 7% (9%–5%) risk reduction for each additional cup of coffee per day 25% (18%–31%) risk reduction for consumption of 3–4 cups of coffee per day</td>
</tr>
<tr>
<td>Meta-analysis of 6 cohort studies</td>
<td>225,516</td>
<td>Generally healthy</td>
<td>8.4–12 y</td>
<td>Incident T2DM RR=0.64 ($0.54$–$0.77$) for 3–4 cups/d of decaffeinated coffee</td>
<td></td>
</tr>
<tr>
<td>Zhang (2011)59</td>
<td>Meta-analysis of 6 cohort studies</td>
<td>172,567</td>
<td>Generally healthy</td>
<td>6.4–33 y</td>
<td>Incident hypertension Habitual coffee consumption of &gt;3 cups/d was not associated with an increased risk of hypertension compared with &lt;1 cup/d Slightly elevated risk associated with light-to-moderate consumption of 1–3 cups/d (RR for comparison of 3 with 0 cups/d: $1.07$ ($0.97$–$1.20$)</td>
</tr>
</tbody>
</table>

CHD indicates coronary heart disease; CI, 95% confidence interval; CVD, cardiovascular disease; DBP, diastolic blood pressure; FMD, flow-mediated dilatation; GI, glycemic index; HC, hypercholesterolemia; HOMA-IR, insulin resistance index; RCT, randomized, controlled trial; RR, relative risk; SBP, systolic blood pressure; SMD, standardized mean difference; and T2DM, type 2 diabetes mellitus.

*Risk ratios in meta-analyses of epidemiological studies, usually adjusted for multiple confounders, are for highest versus lowest categories of consumption or increased servings per day, as specified. Outcome changes (Δ) are means for average doses of seeds or seed products in seed diets in comparison with control diets in meta-analyses of RCTs; only statistically significant changes are shown. Values between parentheses are 95% confidence intervals.

†SMDs are interpreted as follows: <0.4, small effect size; 0.4–0.7, moderate effect size; and >0.7, large effect size.
Nuts (Tree Nuts and Peanuts)

Over the past 2 decades, 4 large prospective studies in the United States have reported on incident CHD in relation to frequency of nut consumption (including peanuts and peanut butter). As summarized in a pooled analysis, the results have consistently shown protection from CHD in participants who ate nuts at least twice per week in comparison with those who never or rarely consumed nuts (Table 3). Frequent nut consumption also relates inversely to total mortality, as suggested by recent reports from a large Dutch cohort and the Nurses’ Health Study. As reviewed, in the Physician’s Health Study, nut consumption was related to lower rates of sudden cardiac death, but not of stroke, heart failure, or atrial fibrillation; 2 other studies reported that nut and peanut intake was associated with a reduced risk of T2DM in women, but not in men.

More than 50 short-term RCTs have compared the effects of nut-enriched and nut-free diets on blood lipids and lipoproteins. A meta-analysis of 13 walnut-feeding studies and a recent pooled analysis of 25 RCTs using various nuts indicate a consistent cholesterol-lowering effect (Table 3). In the pooled analysis LDL-cholesterol was reduced by 7.4% for an average consumption of 67 g (2.4 oz) of nuts depending on nut dose and baseline LDL-cholesterol, and was similar by sex and age group and independent of the type of nut tested. Acute feeding studies indicate that nuts reduce postprandial glucose responses when consumed with foods having a high glycemic index, which suggests that they may be useful in diabetic control. Importantly, recent evidence from the PREvención con DIeta MEDiterránea (PREDIMED) intervention trial in Spanish subjects at high cardiovascular risk showed that a Mediterranean diet with 1 daily serving of mixed nuts reduced incident T2DM by 52% (95% confidence interval [CI], 4%-76%) after 4 years in comparison with a control diet. Limited evidence from RCTs suggests that nuts, particularly walnuts, have beneficial effects on blood pressure and endothelial function. Nut-feeding studies have also documented reduced circulating concentrations of inflammatory cytokines but no consistent changes of C-reactive protein. Finally, despite the high energy density of nuts, there is no evidence that their frequent consumption promotes obesity, probably because of a prominent satiating effect. In the PREDIMED trial, the Mediterranean diet supplemented with nuts significantly reduced the prevalence of metabolic syndrome in comparison with the control diet after a 1-year follow-up, mainly by reducing waist circumference.

Recently, the final results of the landmark PREDIMED RCT have been published showing for the first time a reduction of incident CVD after long-term consumption of a diet enriched in seeds. The PREDIMED study was a multicenter, nutrition intervention, primary prevention trial conducted in Spain wherein nearly 7500 participants at high cardiovascular risk, but with no cardiovascular disease at enrollment, were randomly assigned to 1 of 3 diets: a Mediterranean diet supplemented with daily doses of 30 g of mixed nuts (15 g walnuts, 7.5 g almonds, and 7.5 g hazelnuts), a Mediterranean diet supplemented with extravirgin olive oil (1 L/wk), or a control diet (advice to reduce dietary fat). After a median follow-up of 4.8 years, the participants in the 2 Mediterranean diet groups showed a 30% reduction in CVD events (myocardial infarction, stroke, or cardiovascular death) in comparison with the control diet. The nut diet was also associated with a significant 49% reduction in risk of stroke. Of note, the interventions were intended to improve the overall dietary pattern, but the major between-group differences in food intake were for the supplemental items. Thus, nuts were probably responsible for most of the observed benefits in the Mediterranean diet with nuts group. The results of the PREDIMED trial show the full potential of nuts and other healthy foods such as extravirgin olive oil to improve cardiovascular health.

Pulses

Two studies have examined the association between pulse consumption and risk of CVD. In the First National Health and Nutrition Examination Survey (NHANES) Epidemiological Follow-up Study, frequency of pulse plus peanut and peanut butter consumption was inversely associated with the incidence of CHD and CVD during a 19-year follow-up. Legume consumption ≥4/wk compared with <1/wk was associated with a 22% lower risk of CHD (adjusted risk ratio [RR] 0.78; 95% CI, 0.68–0.90) and an 11% lower risk of CVD (adjusted RR 0.89; 95% CI, 0.80–0.98). A case-control study conducted in Costa Rica, where dry beans are a staple, compared bean intake in 2119 survivors of a first acute myocardial infarction with matched population controls. In comparison with nonconsumers, 1 serving of beans per day was inversely associated with myocardial infarction, with an adjusted odds ratio of 0.62 (95% CI, 0.45–0.88). In another report on that study’s control population, substituting 1 serving of beans for 1 serving of white rice was associated with a 35% (95% CI, 15%–50%) lower risk of having the metabolic syndrome, related mainly to a decreased frequency of low high-density lipoprotein cholesterol and high fasting glucose. Similar findings were reported from NHANES 1999–2002; in comparison with nonconsumers, bean consumers had significantly lower body weight, smaller waist circumference, and lower systolic blood pressure. The risk of T2DM associated with pulse consumption has not been specifically assessed in epidemiological studies. However, pulses are an important component of dietary patterns clearly related to a lower T2DM risk, such as low–glycemic index, high-fiber, and Mediterranean diets.

Studies dating back to the 1980s showed that daily servings of pulses had a beneficial effect on the lipid profile. A recent updated meta-analysis of 10 RCTs evaluating the effects of pulse consumption on cholesterol levels indicates that a pulse-rich diet significantly decreases total cholesterol and LDL-cholesterol, with nonsignificant increases in...
high-density lipoprotein cholesterol and reductions in triglycerides (Table 3). A meta-analysis on glucose metabolism indicates that pulses, alone or in low–glycemic index or high-fiber diets, modestly improve medium- to longer-term glycemic control in subjects with or without T2DM. Acute feeding studies indicate that pulses, like nuts, reduce postprandial glucose responses in comparison with higher-glycemic index foods, further suggesting a beneficial impact on diabetic control.

**Cocoa and Chocolate**

Six recent cohort studies have reported on incident CVD in relation to the frequency of chocolate consumption (Table 3). Larsson et al reported lower stroke incidence associated with chocolate consumption and performed another meta-analysis that confirmed its protective effect. Two of the cohort studies included in the first meta-analysis on CVD outcomes also reported that blood pressure was significantly lower in the highest category of chocolate consumption. A prospective study evaluated the association between chocolate consumption and T2DM and reported a beneficial effect. A common problem is that different types of chocolate (dark versus milk versus white) were not distinguished in epidemiological studies. Even though the composition of chocolate is highly variable and diverges significantly from that of the original seed, it is the cocoa product most widely consumed. For this reason, most epidemiological studies analyzed consumption of any type of chocolate as an exposure variable.

A number of small RCTs assessing the short-term effects of dark chocolate or other cocoa products on serum lipids, blood pressure, or other intermediate markers of CVD have been published in the past decade (Table 3). Some used isolated flavanols, a subclass of flavonoid phenolics believed to be the principal bioactive component of cocoa. The effect sizes on lipids and blood pressure differ among meta-analyses, although the direction of the effects is consistently beneficial. These findings need to be confirmed in larger, longer, well-controlled feeding studies. On the other hand, a meta-analysis indicates a clear benefit of cocoa products on insulin resistance. Also, endothelial function was improved in both acute and chronic studies without evidence of heterogeneity between trials. Subgroup analyses indicated stronger benefit in participants at high risk of CVD than in healthy subjects for many outcomes. There is also RCT evidence that acute consumption of dark chocolate induces coronary vasodilation. Isolated flavanols, a subclass of flavonoid phenolics believed to be the principal bioactive component of cocoa, the effect sizes on lipids and blood pressure differ among meta-analyses, although the direction of the effects is consistently beneficial. These findings need to be confirmed in larger, longer, well-controlled feeding studies. On the other hand, a meta-analysis indicates a clear benefit of cocoa products on insulin resistance. Also, endothelial function was improved in both acute and chronic studies without evidence of heterogeneity between trials. Subgroup analyses indicated stronger benefit in participants at high risk of CVD than in healthy subjects for many outcomes. There is also RCT evidence that acute consumption of dark chocolate induces coronary vasodilation. Flavonoids are known to have antioxidant, anti-inflammatory, and platelet aggregating properties. Importantly, there is a negligible risk of weight gain despite the high-energy content of chocolate, probably related to high satiation.

**Coffee**

Coffee has been extensively studied in relation to various diseases, including CVD and T2DM. In Wu et al’s meta-analysis of 21 prospective cohort studies on coffee and risk of CHD, there was no overall increased risk with greater consumption. Among women, but not men, there was an indication of an inverse association for moderate amount of coffee consumption (2–4 cups/d) and risk of CHD (Table 3). In a meta-analysis of coffee consumption and risk of stroke, in comparison with nonconsumers, consumption of 1 to 6 cups/d was inversely associated with risk of stroke, with the strongest association (17% lower risk) for 3 to 4 cups/d. Mostofsky et al conducted a meta-analysis of 5 prospective studies of coffee and heart failure and observed the lowest risk for consumption of 4 cups/d. These meta-analyses suggest a J-shaped relationship between coffee consumption and the incidence of CHD, stroke, and heart failure, with modest benefit associated with moderate consumption (3–4 cups/d).

In 2005, van Dam and Hu conducted a meta-analysis of 9 cohort studies of coffee consumption and risk of T2DM, including 193,473 participants and 8394 incident cases. The RR of T2DM was 0.65 (95% CI, 0.54–0.78) for the highest (6 or 7 cups/d) and 0.72 (95% CI, 0.62–0.83) for the second highest (4–6 cups/d) category of coffee consumption in comparison with the lowest consumption category (0 or 2 cups/d). In 2009, Huxley et al updated the meta-analysis with 18 similar cohort studies. Overall, each additional cup of coffee per day was associated with a 7% reduction in the incidence of T2DM after adjustment for potential confounders. Risk reduction was 27% for consumers of 3 to 4 cups of total coffee per day and 36% for a similar consumption of decaffeinated coffee.

Habitual consumption of unfiltered coffee, such as French pressed and boiled coffee, has been shown to increase total and LDL-cholesterol concentrations because of the high concentrations of the cholesterol-raising compound cafestol. Paper-filtered or instant coffees do not appear to have cholesterol-raising effects. In addition, acute caffeine intake raises blood pressure, but habitual consumption has much smaller or no effects in normotensive or hypertensive individuals. Moreover, large prospective studies showed no or a modest inverse association between habitual coffee intake and long-term risk of hypertension, likely related to developing tolerance. Furthermore, potential harmful effects of caffeine on blood pressure may be counterbalanced by the beneficial effects of other components, such as polyphenols and minerals.

Several prospective studies have suggested a modest inverse association between coffee and the risk of total and cause-specific mortality. In the American Association of Retired Persons (AARP) Diet and Health Study, adjusted RRs for death among men who drank coffee in comparison with nondrinkers were 0.99 for drinking <1 cup/d; 0.94 for 1 cup; 0.90 for 2 or 3 cups; 0.88 for 4 or 5 cups; and 0.90 for 26 cups of coffee per day (P=0.001 for trend). Corresponding RRs among women were 1.01, 0.95, 0.87, 0.84, and 0.85 (P<0.001 for trend). Inverse associations were observed for deaths attributable to CVD, respiratory disease, diabetes mellitus, and infections, but not for deaths attributable to cancer. Similar results were observed in 2 other large cohort studies, the Health Professionals Follow-up Study and the Nurses’ Health Study. Taken together, large prospective cohort studies have demonstrated that higher consumption of coffee is also associated with a moderately lower mortality risk.

**Mechanisms for Beneficial Effects of Seeds**

The nutrient density in the complex matrices of seeds probably explains the lower CVD risk observed with higher seed consumption. Many of these food constituents synergistically
interact to beneficially affect various metabolic pathways intermediate in CVD and T2DM risk (Figure). We will summarize, in brief, the scientific evidence on the bioactivity of known seed components to provide a mechanistic framework for their cardioprotective benefits.

**Fatty Acids**
Among seeds, nuts and chocolate have the highest total fat content (Table 1). However, with the exception of chocolate (rich in stearic acid), seeds have a low SFA content and most fat is made up of unsaturated fatty acids, with variable proportions of monounsaturated fatty acids and essential PUFAs, such as linoleic and α-linolenic acids, the latter being particularly abundant in walnuts. Although not investigated as much as stearic acid, the predominant fatty acid in cocoa products, does not raise blood cholesterol. On the other hand, substituting SFA with unsaturated fatty acids, either monounsaturated fatty acids or PUFA, improves insulin sensitivity and likely reduces the risk of T2DM (reviewed in4). Thus, by way of salutary effects on lipid and glucose metabolism, the fat fraction of seeds could help reduce the risk of CVD and T2DM.

**Carbohydrate and Fiber**
With the exception of coffee as a beverage, which contains very low amounts of macronutrients, whole seeds are important sources of slow-release carbohydrate and dietary fiber, a nonabsorbable nutrient that has received much attention in nutritional epidemiology. There are 2 main types of dietary fiber: metabolically inert insoluble fiber and bioactive soluble or viscous (gel-forming) fiber, which has cholesterol-lowering properties and reduces postprandial glucose responses after carbohydrate-rich meals. With the exception of oat and barley, rich in soluble β-glucans, whole grains contain little soluble fiber but are rich in insoluble fiber (bran), whereas the main sources of soluble fiber in the usual diet are fruit and vegetables. Observational studies have consistently shown that increased intake of dietary fiber, usually from cereals rather than from fruit and vegetables, is associated with reduced incidence of CVD and T2DM. The reason for this apparent contradiction is that, in epidemiological studies, insoluble fiber cannot easily be dissociated from whole grain foods, which provide many other bioactive phytochemicals associated with beneficial health effects, as discussed here. Dietary fiber may also reduce CVD and T2DM risk through blood pressure reduction, improvement of insulin sensitivity, changes in secretion of various gut hormones that may act as satiety factors, and anti-inflammatory effects.

**Protein**
Seeds are important sources of protein. In large observational studies, increased consumption of plant protein as opposed to animal protein has been consistently associated with a moderate reduction in incident CHD. A mediating factor in protection from CVD by plant protein might be an inverse association with blood pressure. The Optimal Macronutrient Intake Trial to Prevent Heart Disease (OmniHeart) also demonstrated that partial substitution of carbohydrate with protein (about half from plant sources) lowered blood pressure and improved the lipid profile in prehypertensive and hypertensive subjects. Again, it is difficult to dissociate the benefit from the vegetable protein per se from the synergizing effects of other bioactive constituents in the protein-containing foods. Some amino acids in seeds may be particularly relevant to CVD protection, such as l-arginine, which is the substrate for endothelium-derived nitric oxide synthesis, a principal regulator of vascular tone and blood pressure. l-Arginine supplementation improves endothelial function in clinical trials and reduces blood pressure in experimental animal models of hypertension. The l-arginine content of seeds probably contributes to the beneficial vasomotor effects of diets or meals.
enriched with nuts and cocoa products. For instance, in a clinical trial in hypercholesterolemic subjects, a diet containing walnuts (18% of the total energy) improved endothelial function in comparison with a Mediterranean diet, and it was estimated that walnut intake increased dietary l-arginine up to 1.4 g/d, which is close to supplement doses showing vaso-motor effects in clinical studies.

### Sterols

Like all plant foods, seeds are cholesterol-free, but their fatty fraction contains sizeable amounts of chemically related non-cholesterol sterols known as plant sterols or phytosterols, nonnutritive components that play important structural roles in membranes. Relevant for human physiology, phytosterols interfere with cholesterol absorption in the intestinal lumen and thus possess cholesterol-lowering properties.

Phytosterols are established nonpharmacological agents that are useful adjuncts to a healthy diet for helping lower serum total and LDL-cholesterol, resulting in average reductions of 10% at the usually recommended doses of 2 g/d, an effect additive to that of statins. However, at doses up to 2 g/d, the effect of phytosterols is dose-related; doses as low as 400 mg/d, easily achieved with frequent intake of various seed products (Table 2), were shown to significantly influence cholesterol metabolism and reduce LDL-cholesterol by an average 5% in moderately hypercholesterolemic individuals. There is also consistent experimental evidence that phytosterols possess anti-inflammatory properties, although clinical studies have proven inconclusive.

### Minerals

Seeds contain little sodium but are rich in K⁺, Mg²⁺, and Ca²⁺. All 3 are critical in cellular metabolism and many physiological processes, of which blood pressure regulation has been most studied. Whereas high sodium (salt) intake is associated with significantly increased risk of stroke and total CVD, intake of nonsodium minerals generally has the opposite effect. A meta-analysis of prospective studies relating dietary Ca²⁺ intake with risk of CVD showed non-significant reductions of 8% for incident CHD and 14% for incident stroke comparing the highest with the lowest level of dietary Ca²⁺ intake. Two similar meta-analyses have shown a significant inverse association between dietary K⁺ intake and risk of stroke, with a decrease in risk of 21% for every 1.64 g/d or 11% for every 1.0 g/d increase in dietary K⁺ intake. The latter dose of K⁺ can be obtained from combining seed servings in the usual diet (Table 2). The association of dietary K⁺ with lower CHD risk, however, is only suggestive. Concerning dietary Mg²⁺ intake, a meta-analysis of prospective studies by Larsson et al. shows a modest but significant inverse association with stroke risk, with an 8% reduction for an increment of 100 mg/d in intake. Hypertension is the main risk factor for cerebrovascular disease; thus, the stronger beneficial effect of reducing sodium and increasing nonsodium mineral intake from dietary sources on stroke risk than CHD risk is ascribable to reductions of blood pressure.
polyphenols have been shown to lower LDL-cholesterol and their proven antioxidant, vascular, and antiplatelet effects, effects of particular seed molecules. For instance, besides flavonoids or other phenolic compounds on clinical cardiovasculardisease benefit observed in regular consumers.52,53,57–60,80–83,86,87

Conclusions
There is substantial evidence that increased consumption of seeds, including whole grains, nuts, legumes, cocoa products, and coffee, is associated with lower risk of CVD and T2DM or a significant reduction in CVD risk factors such as serum cholesterol or blood pressure. Seeds are made of complex matrices in the outer layer and the germ, rich in minerals (K+, Mg2+, and Ca2+, but little sodium), vitamins (particularly tocopherols and folic acid), phytosterols, polyphenols, and other bioactive phytochemicals, where, among other functions, they serve to protect the plant’s DNA from oxidative stress and thus help perpetuate the species. On the other hand, the endosperm of seeds contains nutritive components to sustain the growth of the embryo, with a variable mixture of essential amino acids and fatty acids. Although some seed components (soluble fiber, unsaturated fatty acids, phytosterols) have the potential to reduce blood cholesterol, the whole seed provides a wide array of bioactive molecules likely to have synergistic effects on health outcomes. However, separating the effects of different components of seeds in epidemiological and clinical studies is exceedingly challenging. There is some evidence that a single component such as fiber may not be as beneficial when it is not consumed as a whole grain.133 Therefore, dietary recommendations should embrace a wide array of seeds as part of a plant-based dietary pattern, instead of putting too much emphasis on individual nutrients.

Implications for Dietary Recommendations
The current dietary strategies for CVD prevention focus primarily on the role of individual macronutrients (eg, fat, carbohydrates, or protein). Although reduction in the percentage of calories from dietary fat intake has been commonly recommended, long-term RCTs have provided no good evidence that reducing dietary fat per se can reduce CVD risk.1,7 Likewise, carbohydrate restriction alone is unlikely to have appreciable long-term impact on CVD. It is now recognized that overfocus on individual nutrients is counterproductive, because it misses the complexities of foods and overall eating patterns. A simpler and more friendly food-based dietary approach should be easier to communicate to the public and to implement in dietary practice. The past decade has seen an expansion of epidemiological and clinical research on the roles of seeds in the prevention of CVD, revolutionizing our thinking about the biological mechanisms that link dietary factors and CVD. Some foods that were thought unhealthy on the basis of fat content (eg, nuts) have become important in lowering serum cholesterol and controlling weight.68 The PREDIMED trial has convincingly demonstrated that a Mediterranean diet supplemented with nuts significantly reduces hard CVD end points.74 In addition, there is compelling evidence that increasing the consumption of whole grains and legumes confers cardioprotective benefits. Therefore, dietary recommendations should encourage substitution of whole grains and legumes for refined grains as part of a healthy diet. Whole grains, nuts, and legumes (but not dark chocolate or coffee owing to insufficient evidence at the time) were included in the American Heart Association report setting goals for health promotion and disease reduction for 2020.131 As reviewed here, current evidence suggests that moderate consumption of coffee and cocoa products can be incorporated into a healthy dietary pattern. The evidence base assembled in this review provides further support for the plant-based dietary patterns recommended by dietary guidelines.132

Mounting evidence from prospective studies indicates that higher intake of polyphenol-rich foods in general and of flavonoid-rich foods in particular is associated with protection from CVD, although potential publication bias and marked heterogeneity in results across studies render the evidence inconclusive. The abundance of polyphenols in dark chocolate and coffee is thought to be responsible for the CVD benefit observed in regular consumers.52,53,57–60,80–83,86,87 A meta-analysis of 113 interventional studies of nearly 6000 subjects given different cocoa products or their pure phenolic extracts demonstrated improvement in various intermediate markers of cardiovascular health, including blood pressure, endothelial function, blood lipids, and insulin sensitivity. Several of the intervention studies reviewed were conducted with pure flavonoids and had effects similar to those elicited by the parent foods, which suggests that the benefit is due, at least in part, to these antioxidant molecules. However, no long-term RCTs have evaluated the effects of flavonoids or other phenolic compounds on clinical cardiovascular end points.

As shown in part in Figure, most bioactive seed components synergize to affect multiple metabolic and vascular physiology pathways leading to protection from CVD and T2DM. For the sake of simplicity, the scheme cannot include all the reported effects of particular seed molecules. For instance, besides their proven antioxidant, vascular, and antiplatelet effects, polyphenols have been shown to lower LDL-cholesterol and improve insulin sensitivity in RCTs.55 The complex bioactivity and multifunctionality of whole seed components supports their important role in a heart-healthy diet.
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References


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