REVIEW ARTICLE

The effect of plant-based diets on thrombotic risk factors

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KEY WORDS

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ABSTRACT

Plant-based diets are considered to improve cardiometabolic health and to protect against cardiovascular disease. Although they center around plant-based foods, they do not necessarily exclude all animal products and comprise of a range of intakes that vary according to the type and the proportion of animal products included. Numerous metabolic pathways have been identified through which plant-based diets can exert beneficial effects including improved body composition, lipid profile, and glucose metabolism and decreased inflammation and blood pressure. Their effects on thrombosis as a cardiovascular disease pathway are, however, less clear. Ample evidence for the effects of individual dietary components of plant-based diets on thrombotic risk factors exists, but the effect of whole diets and / or dietary patterns remains less-well explored with the existing literature reporting inconsistent and inconclusive findings. Here we aim to review the literature describing the effect of different plant-based diets (vegan, lacto-vegetarian, lacto-ovo-vegetarian, pescatarian, and flexitarian) and dietary patterns (Mediterranean, Nordic, Portfolio, and DASH) on specific thrombotic risk factors (fibrinogen, platelets, factor VII, fibrinolysis) in order to better clarify these relationships and to try to explain the apparent discrepant findings. We demonstrate that a one-size-fits-all conclusion cannot be drawn and that the potential antithrombotic effect of different plant-based diets depends on the nutrient composition, the content of active antithrombotic dietary components, the relative absence of prothrombotic dietary factors as well as the degree of total caloric restriction.

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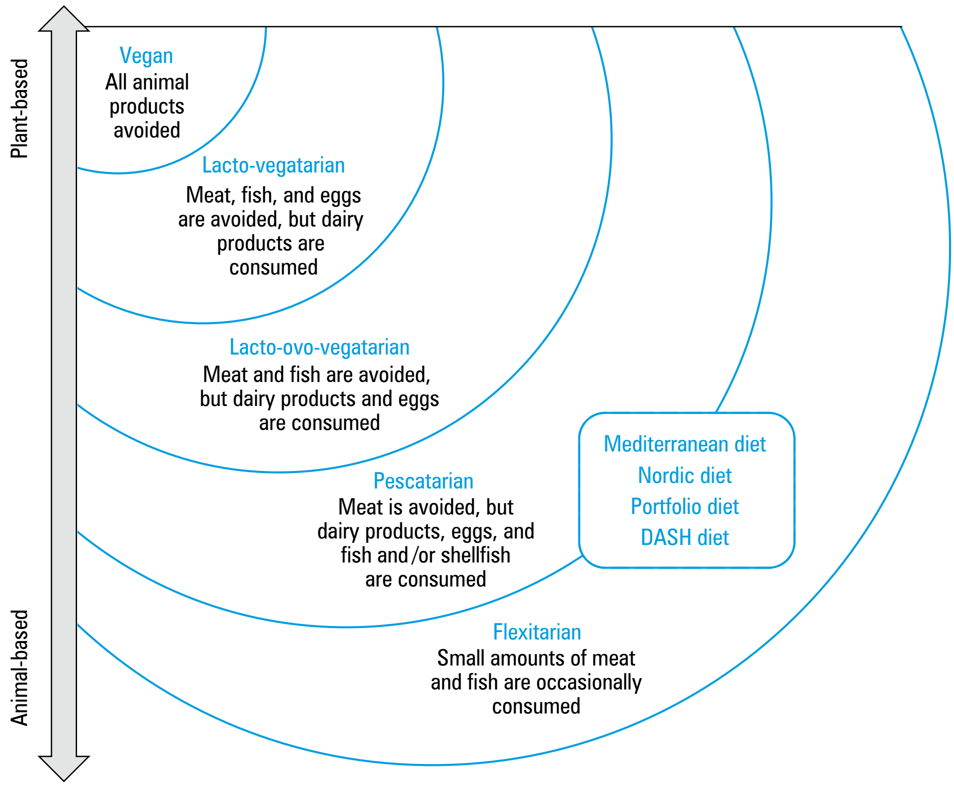
Introduction Plant-based diets primarily contain foods of plant origin, which include not only vegetables and fruit, but also nuts and seeds, legumes and beans, oils, and whole grains. Plant-based diets do not necessarily exclude all animal products and can range from total exclusion (eg, vegan) to meat consumption once to twice a week (eg, flexitarian). The unifying focus is on the consumption of more foods from plant sources proportional to animal-based foods.[1]

Consumption of plant-based diets have been associated with a significant reduction in cardiovascular disease (CVD) risk,[2-4] CVD mortality,[5,6] and also all-cause mortality.[7,8] The beneficial effect of plant-based diets on cardiometabolic health has been attributed to, amongst others, the low caloric density, lower saturated fat, and higher mono- and polyunsaturated fat content, high fiber content as well as its antioxidant and anti-inflammatory compounds.[1]

Randomized control trials and observational studies have identified a number of pathways through which plant-based diets can improve cardiometabolic health. These include a number of risk factors recognized by the European Society of Cardiology guidelines for CVD prevention[9]: reduction of obesity and its downstream sequelae, improved glycemic control and decreased insulin resistance, decreased blood pressure, and an improved lipid profile (reviewed by Kahleova et al[10]). In addition, plant-based diets have been shown to improve other CVD-related pathways such as cessation and reversal of atherosclerotic plaque deposition, decreased inflammation and thrombosis. There is a vast amount of literature investigating the relationship of diet with thrombosis, but most of these studies assessed the effect of individual nutrients or foods such as alcohol, dietary fat, n-3 fatty acid supplementation, fiber, carbohydrates, and a variety of micronutrients

FIGURE 1 Spectrum of plant-based diets (adapted from Kahleova[1])



(vitamins, minerals and phytochemicals) (reviewed by Pieters and De Maat[11]). Much less is known regarding the influence of whole diets—in particular, plant-based diets and dietary patterns—on thrombotic factors such as platelet aggregation, coagulation, and fibrinolysis, with the existing literature reporting inconsistent and inconclusive findings. This is likely the result of the differences in composition of the investigated plant-based diets (ranging from strictly vegan, to diets containing some meat or even high intakes of fish), the specific outcomes measured, and differences in study designs such as randomized controlled trials or observational studies, duration, selection of control groups, and health status of the participants (eg, healthy vs patients with CVD). Here we aim to review the existing literature describing the effect of different plant-based diets (but not the individual constituent nutrients or foods) on specific thrombotic risk factors in order to better clarify these relationships and to try to explain the apparent discrepant findings. The thrombotic factors the review will focus on include platelet function, coagulation proteins (fibrinogen and factor VII [FVII]), and fibrinolysis, as most of the available evidence focuses on these outcomes.

Plant-based diets We first describe the composition of different plant-based diets and dietary patterns in order to better interpret their potential varying effects on the discussed thrombotic factors. The 2021 European Society of Cardiology guidelines on CVD prevention in clinical practice recommend the adoption of a more plant-based and less animal-based food pattern consisting of less than 10% of total energy from saturated fatty acids, less than 5 g of salt, 30 to 45 g of fiber, at least 200 g of fruit, and at least 200 g of vegetables per day. They also recommend red meat consumption of no more than 350 to 500 g per week, with strict minimization of processed meat, (fatty) fish consumption 1 to 2 times per week, 30 g of unsalted nuts per day, no more than 100 g of alcohol per week, and discourage consumption of sugar-sweetened beverages.[9] These guidelines, in essence, describe the underpinning of plant-based diets.

Although plant-based diets center around plant-based foods, they do not necessarily exclude all animal products. Therefore, plant-based eating is comprised of a range of intakes that vary according to the type and the proportion of animal products included in the diet (**FIGURE 1**).

Veganism is considered the purest form of plant-based eating, characterized by the omission of all animal products from the diet as well as foods that are high in fat, salt, and sugar while only whole food of plant origin is consumed. If not carefully planned and well-balanced, vegan diets can lead to deficiencies in, amongst others, long-chain n-3 polyunsaturated fatty acids and vitamin B_{12} because of strict exclusion of animal products.[12] Lacto-vegetarian diets, while excluding meat and fish, include dairy products, whereas lacto-ovo-vegetarian diets include both dairy and eggs while excluding meat and fish.[13] Pescatarian diets, also referred to as pesca-vegetarian diets, include seafood along with eggs and dairy products while other animal products (poultry and red meat) are not consumed.[14] Flexitarian diets, also known as semivegetarian diets, are mainly plant-based but occasionally include meat, dairy and eggs and focus on variety while attempting to minimize animal product consumption.[15]

Within the context of the above-mentioned plant-based diets, a number of specific plant-based dietary patterns that fall within the pescatarian and flexitarian diets (depending on whether only fish or both fish and red meat are consumed) have been investigated, and demonstrated to have cardiometabolic health benefits. These include the Mediterranean, Nordic, Portfolio, and DASH diets.[13]

Mediterranean diet The Mediterranean diet is based on food patterns observed in the early 1950s in Greece, Crete, and the southern parts of Italy. Keys et al[16] noticed in the Seven-Countries Study that individuals who lived in those parts of the world (ie, in those parts of the Mediterranean region) had the lowest cardiovascular mortality rate whilst consuming the largest amount of fat among the countries included in the study.

Traditional practices included: the addition of olive oil to vegetables and legumes to improve their palatability, fruit rather than sweetened foods was eaten as a daily dessert, salads and stews were accompanied by cheeses, while red meat was reserved for special occasions only.[17,18]

Today the diet typically does not limit caloric intake; rather, it accentuates variety and the consumption of plant-based foods with extra virgin, cold-pressed olive oil (up to 8 servings) as its principal fat source. Plant-based foods in the Mediterranean diet include vegetables (3–9 servings), fruit (0.5–2 servings), breads and whole grain cereals (1–13 servings), potatoes, nuts, legumes / pulses, seeds, and beans. Fish, poultry, dairy, and (red) wine are consumed in moderation while red meat, saturated fat, eggs, processed foods, and added sugars are limited.[13,19] It typically contains high amounts of fiber (>30 g/day), around 35% total fat of which 15% to 20% is monounsaturated fat and less than 10% is saturated fat. Daily caloric intake is in the order of 9300 kJ.[20]

Nordic diet The Nordic diet is considered a primarily plant-based diet with animal products used in moderation, mainly as side dishes.[21] Emphasis is placed on traditional Nordic food components, predominantly the healthier options, which are indigenous to and produced locally in the Nordic countries. Some region-specific variation exists such as the type of fish, berries, fruit, vegetables, and bread that are consumed.[22]

The overall dietary pattern is based on 3 fundamental guidelines: 1) more calories from plant-based foods and less from animal-based foods (especially meat), 2) more foods from the sea and lakes, 3) more food from the countryside (indigenous game and vegetation).[23]

Plant-based foods native to the Nordic region include cruciferous vegetables (mainly cabbage), root vegetables (like potatoes), berries (such as bilberries, lingonberries, strawberries, blueberries, cowberries, and cloudberries) and other fruit (like apples and pears), cereals (oats, barley, whole grain, and rye bread) as well as legumes. The long coastline provides a rich source of fatty fish (salmon and herring) and other seafood (shellfish and seaweed). Lean game meat (venison, goose, duck) and low-fat dairy is also incorporated in the diet.[13,24-28]

Like the Mediterranean diet, the Nordic diet promotes the consumption of vegetables and fruit, whole grains, and fish, while restricting the use of saturated fat as well as red meat and processed foods. Instead of olive oil as in the Mediterranean diet, rapeseed oil (also known as canola oil) is used as the source of unsaturated fat.[22]

Portfolio diet Another plant-based dietary pattern is the Portfolio diet, which was first formulated in the early 2000s. It consists of a "portfolio" of 4 core food components (all plant-based) that are known to lower cholesterol, namely: 1) nuts (tree nuts or peanuts); 2) plant-based protein (soy products, lentils, beans, chickpeas and other legumes); 3) viscous soluble fiber from fruit (apples, oranges, berries), grains (oats, barley, psyllium) and / or vegetables (eggplant, okra); and 4) plant sterols (predominantly plant sterol-enriched margarine).[13,29-33]

Jenkins et al[34] proposed an enhanced Portfolio diet in which carbohydrates are replaced by monounsaturated fat, which is then added to the established 4 components of the original Portfolio diet to provide around 25% of energy.

DASH diet The DASH diet, an acronym for "Dietary Approach to Stop Hypertension," is based on the benefits of a plant-based diet on blood pressure. This dietary pattern was designed to both treat and prevent hypertension.[35,36] The design goal for the DASH diet was to establish plant-based patterns associated with lowering blood pressure while still incorporating a sufficient amount of animal-based products to ensure palatability of the diet for nonvegetarian users.[36]

This dietary pattern is low in fat and rich in carbohydrates. It encourages the intake of fruit, vegetables, whole grains, nuts, and legumes while fish, poultry, and dairy products (fat-free or low-fat) are consumed in moderation and dietary cholesterol, total and saturated fat, red meat, processed and refined foods with added sugars are minimized.[13,37,38] Compared with regular omnivorous diets, the DASH diet provides more protein, fiber, magnesium, calcium, and potassium.[39]

Healthy vs unhealthy plant-based diets It is important to note that not all plant-based diets are healthy. Diets high in sugary drinks, refined carbohydrates, and sweets are also plant-based, but are not considered healthy nor do they have any protective effects in terms of CVD.[6,40] Healthy plant-based diets, therefore, contain high-quality whole plant foods that are typically rich in dietary fiber, antioxidants, unsaturated fatty acids, and micronutrients. Unhealthy plant-based diets, on the contrary, typically have a higher glycemic index and load, reduced fiber content, lower micronutrient and higher calorie content, and contain more processed foods.[40]

For this review, we used combinations of the following keywords in our search strings: *plant-based diets*, *vegetarian*, *Mediterranean diet*, *DASH diet*, *Portfolio diet*, *Nordic diet* and *thrombosis*, *hemostasis*, *coagulation*, *fibrinogen*, *fibrinolysis*, and *platelet** (*function*, *aggregation*). We found 26 articles that fit the inclusion criteria which will be discussed in the following sections according to the respective thrombotic factors.

Plant-based diets and fibrinogen Fifteen studies investigated the association between plant-based diets and fibrinogen (TABLE 1), 10 of which were cross-sectional investigations and 5 were interventions. Of the 10 cross-sectional studies, 5 reported lower fibrinogen concentration in plant-based diet consumers (ranging from vegan to flexitarian)[41-45] and 5 reported no difference[46-50] compared with omnivores. Two studies reported an inverse association between fibrinogen concentration and plant protein and fiber intake[44,48] and one an inverse association with the adherence to the Mediterranean dietary pattern.[41] One study also reported a positive association between fibrinogen concentration and food patterns containing high intakes of red meat, low-fiber bread, and dairy products.[45] The potential beneficial effect of habitual consumption of plant-based diets on fibrinogen concentration has been attributed to lower intakes of saturated fats and higher intakes of non-nutritive components, fish oil (in flexitarian and pescatarian diets) as well as the tendency for vegetarians to have a more-healthy body mass index—all which have been linked to fibrinogen concentration.[51,52] None of the intervention studies ranging from 2 weeks to 6 months, however, demonstrated a beneficial effect of plant-based diets on reducing fibrinogen concentration.[53-57] One study reported an increase in fibrinogen concentration, but this was related to a significant decrease in body mass index.[54] Increased fibrinogen during rapid weight loss has been ascribed to a parallel increase in fatty acids which stimulate hepatic fibrinogen production.[58] Furthermore, James et al[44] previously reported that both under- and overnutrition were associated with higher fibrinogen and that dietary guidelines should therefore focus on preventing overnutrition and its consequences such as noncommunicable diseases, but also they should not be too limiting which could result in undernutrition. In a previous review,[59] we concluded that the direct effects of the diet on fibrinogen concentration is likely modest, which is in agreement with the lack of effect observed in the intervention studies, but if the diet results in longer-term health consequences, such as obesity, insulin resistance or diabetes, the effects become more pronounced.

Plant-based diets and platelets The effect of plant-based diets on platelet function is varied, as summarized in TABLE 2. Two of the 6 cross-sectional studies investigating the association between different plant-based diets and platelets found increased platelet aggregation / function in vegetarians compared with omnivores.[43,49] Three studies found no difference[47,60,61] and a single report inhibited platelet activity measured as lower concentrations of platelet-derived microparticles in individuals consuming a Nordic diet.[28] There were also no consistent effects in the 4 intervention studies with durations ranging from 2 weeks to 6 months. Two of the studies (vegetarian and Mediterranean diet [with and without wine]) found increased platelet aggregation with at least one platelet agonist, while no difference in platelet function was reported with other agonists used.[62,63] Two studies comparing the DASH diet to a control diet reported decreased platelet activation.[64,65] In contrast to plant-based diets, Mann et al[63] found red and white meat not to affect platelet function while fish consumption resulted in a decreased collagen-stimulated platelet thromboxane production but did not affect platelet aggregation.

This lack of consistency in findings is not entirely surprising given the variation in platelet function outcomes measured (ex vivo platelet aggregation, thromboxane secretion, plasma microvesicle concentration), type and concentration of agonists used (adenosine diphosphate, collagen, epinephrine, arachidonic acid), and platelet concentration in the analyzed sample (whole blood, platelet-rich plasma, platelet-adjusted plasma). In addition, the dietary interventions considered to be plant-based ranged from strictly vegan to diets containing occasional consumption of white meat and fish (DASH) and diets with high intakes of fatty fish such as the Nordic diet and, in the case of the Mediterranean diet, also containing moderate amounts of alcohol, particularly red wine. Different components of plant-based diets have been reported to have varying effects on platelet function and inclusion / exclusion of these dietary components in the study diets will therefore differentially influence the outcome of the platelet function tests. A detailed discussion of the effects of these nutrients and foods on platelet function has been published in a number of reviews.[11,12,66-74] While discussing the evidence for the individual nutrients and foods is outside the scope of this review, we aim to provide a broad overview of different components of plant-based diets that may influence platelet function, highlighting the complexity of drawing conclusions regarding the effect of plant-based diets on platelet function.

Foods and nutrients typically included in plant-based diets such as dark chocolate, foods with a low glycemic index, garlic, ginger, onion, grapes (and juice), berries, tomato, vitamins, minerals, and phytochemicals (flavonoids and antioxidants) have all been shown to reduce platelet aggregation

TABLE 1 Fibrinogen and plant-based diets (continued on the next pages)

No.	Study	Study population	Type of diet	Biomarker	Main results
Cross-sectional					
1	Corley et al[41]; the Lothian Birth Cohort 1936	792 participants (383 men and 409 women; mean age, 69.5 y); CRP >10 mg/ml excluded; Scotland	Food patterns associated with outcomes identified using principle component analysis: • Mediterranean • Health-aware (high intake of fruit and carrots; low intake of meat, egg, spirits, and liqueurs)	Fibrinogen (Clauss)	Fibrinogen was inversely associated with the Mediterranean dietary pattern, fruit intake and combined fruit and vegetable intake.
2	Famodu et al[42]; selection based on habitual intakes	76 participants: • 8 vegans (mean age, 47.1 y) • 28 lacto-ovo-vegetarians (mean age, 49 y) • 40 omnivores (age- and BMI--matched; mean age, 48 y); no comorbidities; Nigeria	• Vegan • Lacto-ovo-vegetarian • Omnivore (habitual African diet)	Fibrinogen (clot weight)	• Fibrinogen was significantly higher in the omnivorous control group compared with lacto-ovo--vegetarians and vegans. • Fibrinogen was significantly lower in the vegan group compared with lacto-ovo--vegetarians.
3	Mezzano et al[43]	54 participants with no comorbidities: • 26 vegetarians (12 men, 14 women) = 3 vegans and 23 lacto-vegetarians/lacto-ovo--vegetarians (mean age, 39 y) • 26 omnivores (age-, sex-, and socioeconomic status–matched); Chile	• Vegetarian (vegan and lacto-vegetarian/lacto-ovo--vegetarian) • Omnivore • >1 year on diet	Fibrinogen (Clauss)	Fibrinogen was significantly lower in the vegetarian group compared with omnivorous controls.
4	Pan et al[46]	114 participants with no comorbidities: • 55 Buddhist vegetarians (23 men, 32 women) • 59 omnivores (20 men, 39 women); age, 20–30 y; Chinese participants	• Vegetarian (no fish or meat) • Omnivore • >2 years on the diet	Fibrinogen (Clauss)	No significant difference in fibrinogen between the vegetarians and omnivores
5	Suwannuruks et al[47]	80 participants: • 30 vegans (15 men, 15 women) • 10 lacto-vegetarians • 10 lacto-ovo-vegetarians • 30 omnivores (not matched; 15 men, 15 women); no comorbidities; age, 18–50 y; Thailand	• Vegetarian (vegan, lacto--vegetarian, lacto-ovo--vegetarian) • Omnivore • >4 years on diet	Fibrinogen (the Ellis and Stransky method, 1961)	No significant difference in fibrinogen concentration between the vegetarians and omnivores
6	Mia and Vorster[48]	321 Indian adolescents: • 31 lacto-ovo-vegetarian (11 men, 20 women) • 290 omnivores (148 men, 142 women); age, 16–18 y; South Africa	• Lacto-ovo-vegetarian • Omnivore The Indian vegetarian diet was not lower in fat (>40% TE in both groups) or higher in fiber than the omnivore diet.	Fibrinogen (Clauss)	• Fibrinogen concentration did not differ between the lacto-ovo--vegetarians and the omnivores. • Fibrinogen showed significantly negative correlations with intakes of plant protein and dietary fiber. • The number of vegetarians in this study was small (10%) and the results therefore cannot be extrapolated to the general vegetarian population.
7	THUSA[44]	1854 apparently healthy African men and women; age, >15 y; South Africa	The paper investigated the association between nutrient intakes, nutritional status, and fibrinogen concentration. Dietary intakes ranged from traditional low--fat African diet to more Westernized diets.	Fibrinogen (Clauss)	Participants with the highest intake of dietary fiber and plant protein and with the lowest intake of trans fatty acids and animal protein had the lowest plasma fibrinogen concentration.

TABLE 1 Fibrinogen and plant-based diets (continued on the next page)

No.	Study	Study population	Type of diet	Biomarker	Main results
8	Liese et al[45]; the Insulin Resistance Atherosclerosis Study	880 middle-aged adults, 144 with diabetes mellitus; age, 45–74 y; African American, Hispanic, and non-Hispanic White participants; USA	Identification of food patterns associated with fibrinogen using reduced rank regression	Fibrinogen (modified clot-rate assay, Diagnostica STAGO)	Fibrinogen had a positive association with the food pattern containing high intake of red meat, low-fiber bread and cereal, dried beans, fried potatoes, tomato vegetables, eggs, cheese and cottage cheese and low intake of wine.
9	Li et al[49]	139 healthy men; age, 20–50 y: • 18 vegans • 43 lacto-ovo-vegetarians • 60 moderate meat-eaters • 18 high meat-eaters; nonsmoking	• Habitual intakes (at least 6 months prior to study) • Vegan • Lacto-ovo-vegetarian • Moderate meat-eaters (<285 g/day) • High meat-eaters (>285 g/day)	Fibrinogen (Clauss)	Fibrinogen did not differ between the 4 dietary groups.
10	Haines et al[50]; controls were from the Northwick Park Heart Study	332 nonsmokers, not using oral contraception; age, 18–65 y: • 282 omnivores (211 men, 71 women) • 50 vegetarians (27 vegan, 23 lacto-ovo-vegetarian; 25 men, 25 women)	• Vegetarian (vegan and lacto-ovo-vegetarian) • Omnivore	Fibrinogen (method of Fearnley and Chakrabarti)	There was no significant difference in fibrinogen between the vegetarians and omnivores.
Intervention					
11	Kahleova et al[53]; a 24-week randomized, parallel study (diet and exercise interventions) • First 12 weeks: diet-only intervention • Second 12 weeks: aerobic exercise added	74 participants (35 men and 39 women) with type 2 diabetes: 37 vegetarians and 37 controls; age, 30–70 y; Czech Republic	• Vegetarian diet. Animal products were limited to maximum of one portion of low-fat yogurt a day. • Control = conventional diabetic diet • Both diets were isocalorically energy-restricted. Vitamin B_{12} was supplemented in both the experimental and the control group (50 µg/day).	Fibrinogen	There was no significant difference in fibrinogen after the first 12-week diet-only intervention in either group. Fibrinogen was, however, significantly decreased at the end of the 24-week intervention period following the addition of 12 weeks of aerobic exercise. This decrease did not differ significantly between the vegetarian and the conventional diabetic diet groups.
12	Chainani-Wu et al[54]; a 3-month prospective cohort study nested within a larger cohort (Multisite Cardiac Lifestyle Intervention Program)	125 participants: • 54 CHD patients (35 men, 19 women) • 71 high-risk CHD patients (16 men, 55 women); United States (>90% White)	A comprehensive lifestyle intervention that included a low-fat, whole-foods, plant-based diet, exercise, stress management, and group support meetings. The dietary guidelines prescribed included approximately 10% of daily calories from fat, 15% from protein, and 75% from complex carbohydrates.	Fibrinogen	Significant increase in fibrinogen was observed in the high-risk CHD group. This increase was inversely correlated to changes in BMI. No change in fibrinogen concentration in the CHD group.
13	Brestrich et al[55]; (article in German, data were taken from the abstract); intervention with the average duration of 24.2 days	302 participants: • 151 followed a lacto-vegetarian diet • 151 followed the omnivorous control diet	• Lacto-vegetarian diet • Conventional, fat-modified and cholesterol-lowered omnivore diet	Fibrinogen	There was no diet-related change in fibrinogen concentration in either the lacto-vegetarian or the omnivore group.

TABLE 1 Fibrinogen and plant-based diets (continued from the previous pages)

No.	Study	Study population	Type of diet	Biomarker	Main results
14	Marckmann et al[56]; a randomized cross--over study with intervention duration of 2 weeks and a 2-to-6-week washout period	20 healthy women; age, 21–52 y; BMI, 20–25 kg/m^2	3 ad libitum experimental diets: • a starch-rich diet (STARCH), composed according to the Nordic Nutrition Recommendations: <30 E% total fat; <10 E% saturated fatty acids; and >3 g/MJ fiber • a sucrose-rich diet (SUCROSE), resembling the STARCH diet except for the inclusion of additional sucrose (approximately +20 E%, or 120 g sucrose per 10 MJ) in the place of starchy foods (primarily bread, rice, pasta, and cereals) • a high-fat diet (FAT) that had a fat content of 45–50 E% and a dominance of saturated fatty acids The experimental diets were identical with respect to fish and marine n-3 poly-unsaturated fatty acid content.	Fibrinogen (Clauss)	Plasma fibrinogen was not significantly affected by any of the diets.
15	Marckmann et al[57]; a 2-week randomized, crossover study	21 healthy middle-aged individuals: • 11 women (5 postmenopausal; mean age, 52 y) • 10 men (mean age, 53 y); 5 light smokers; Denmark	• Nordic nutrition recommendations: low-fat (28% of energy), high fiber (3.3 g/MJ). Larger amounts of fish, bread and cereals, vegetables and fruit. Energy, 10.4 MJ • Average Danish diet (Dane diet): high-fat diet (39% of energy), low-fiber. Energy, 10.5 MJ	Fibrinogen (Clauss)	Fibrinogen concentration was unaffected by the dietary change.

Abbreviations: BMI, body mass index; CHD, coronary heart disease; CRP, C-reactive protein; E%, percentage of total energy

(reviewed by McEwen,[67] Pieters and De Maat,[11] Dutta-Roy,[69] Tubek et al,[71] and Phang et al[68]). However, whether these changes are sufficient to alter thrombotic status is difficult to determine, as many of the micronutrients have limited bioavailability. The impact of alcohol (as the key component of the Mediterranean diet), on the other hand, is more complex and not yet fully elucidated, with a number of studies demonstrating inhibition of platelet activation, while evidence for enhanced platelet activation has also been reported (reviewed by Pieters and De Maat[11]).

Another important component of plant-based diets is the type of fat consumed with typically proportionally higher intakes of monounsaturated fatty acids (olive oil) and varying ratios of n-3 to n-6 polyunsaturated fatty acids. Vegans have low intakes of long-chain n-3 polyunsaturated fatty acids while flexitarian / pescatarian diets, such as the Nordic diet, containing fatty fish, have a high content. The influence of monounsaturated fatty acids on platelet function remains unclear with several studies reporting inhibited platelet aggregation, others reporting no effect, and others even found increased aggregability (reviewed by Rajaram[66] and Pieters and De Maat[11]). The effect of polyunsaturated fatty acids on platelet function is largely dependent on being either n-3 or n-6, with n-3 inhibiting and n-6 promoting platelet aggregation by competing for cyclooxygenase and lipoxygenase and in doing so, producing different eicosanoids (reviewed by Dutta-Roy[69]). Compared with omnivores, vegetarians, especially vegans, have lower n-3 polyunsaturated fatty acid levels in the platelet membrane phospholipids, which are associated with increased collagen and adenosine diphosphate–stimulated ex vivo blood platelet aggregation (reviewed by Li[12]). Fish consumers, on the other hand, have high n-3 polyunsaturated fatty acid levels. Although the ability of fish oil to modulate platelet function by attenuating thromboxane A_2 production is well known, supplementation studies did not consistently find inhibited platelet aggregation. A meta-analysis of randomized controlled trials concluded that the supplementation of n-3 polyunsaturated fatty acids was associated with a reduced platelet aggregation in

TABLE 2 Platelets and plant-based diets (continued on the next page)

No.	Author	Study population	Type of diet	Biomarker	Main results
Cross-sectional					
1	Mezzano et al[43]	54 participants with no comorbidities: • 26 vegetarians (12 men, 14 women) = 3 vegan and 23 lacto-vegetarian/lacto-ovo-vegetarian; mean age, 39 y) • 26 omnivores (age-, sex-, and socioeconomic status–matched); Chile	• Vegetarian (vegan and lacto-vegetarian/lacto-ovo-vegetarian) • Omnivore • >1 year on diet	• Platelet count • In vitro platelet function (aggregation and secretion)	Vegetarians had significantly higher blood platelet count and in vitro platelet function (aggregation and secretion) than omnivores.
2	Li et al[49]	139 healthy men, age, 20–50 y: • 18 vegans • 43 lacto-ovo-vegetarian • 60 moderate meat-eaters • 18 high meat-eaters; nonsmoking	• Habitual intakes (at least 6 months prior to study) • Vegan • Lacto-ovo-vegetarian • Moderate meat-eaters (<285 g/day) • High meat-eaters (>285 g/day)	• Collagen and ADP-induced whole blood platelet aggregation • Mean platelet volume	• Vegetarians, especially vegans, had significantly increased whole blood platelet aggregation compared with meat-eaters. • The vegan group had a significantly higher mean platelet volume than the other 3 dietary groups.
3	Fisher et al[60]	50 participants: • 10 vegans • 15 lacto-ovo-vegetarian • 25 omnivores (age- and sex-matched)	• Vegetarian: vegan and lacto-ovo-vegetarian • Omnivore	Platelet aggregation (ADP, collagen, epinephrine and arachidonic acid) in platelet-adjusted plasma ($250–350 \times 10^9$ platelets/l)	Platelet aggregation did not differ between the vegetarians and omnivores.
4	Chiva-Blanch et al[28]; Omega-3 Fatty Acids in Elderly Patients with Myocardial Infarction study	174 patients, 2–8 weeks following AMI; age, 70–82 y; standard medication	Dietary patterns determined from habitual intake. High to low adherence to the Nordic diet (3 groups)	Platelet-derived microvesicle quantification	A high adherence to the Nordic diet was associated with lower levels of platelet activation, as determined by a lower plasma concentration of platelet-derived microvesicles.
5	Sanders and Roshanai[61]	40 participants with no comorbidities: • 20 vegans (10 men, 10 women) • 20 omnivores (10 men, 10 women; age- and sex-matched); No medication; England	• Vegan • Omnivore • >1 year on diet • Energy intake was similar, while vegans consumed less protein and fat than the omnivores and more carbohydrates and double the amount of fiber.	ADP, collagen and U44 619 (thromboxane A_2 mimetic)-induced platelet aggregation using platelet-adjusted plasma (2.5×10^8 platelets/l)	Platelet aggregation induced by ADP, compound U44619, and collagen were similar in both groups.
6	Suwannuruks et al[47]	80 participants: • 30 vegans (15 men, 15 women) • 10 lacto-vegetarians • 10 lacto-ovo-vegetarians • 30 omnivores (not matched; 15 men, 15 women); No comorbidities; age, 18–50 y; Thailand	• Vegan • Lacto-vegetarian • Lacto-ovo-vegetarian • Omnivore • >4 years on diet	Platelet aggregation (ADP, collagen, and adrenaline)	No significant difference in platelet aggregation between the vegan, lacto-vegetarian, lacto-ovo-vegetarians and omnivores

TABLE 2 Platelets and plant-based diets (continued from the previous page)

No.	Author	Study population	Type of diet	Biomarker	Main results
Intervention					
7	Mezzano et al[62]; a 90-day parallel study	42 healthy men (mean age, 22 y): • 21 MD • 21 HFD Chile	• Alcohol-free MD • HFD • Fats supplied 27.3% and 39.9% of energy for MD and HFD, respectively. • White meat, fish and legumes were the main source of proteins in MD, whereas HFD was rich in red meat and low in fish. • Isoenergetic supplementation with 240 ml/day of red wine from day 31 to day 60	• Platelet aggregation (ADP, collagen, sodium arachidonate) in platelet-rich plasma • Serotonin secretion in platelet-rich plasma	• There was no significant difference in platelet responses to ADP, collagen or arachidonate between the MD and HFD groups. Intake of the MD was, however, associated with a slightly increased platelet serotonin secretion after stimulation with epinephrine. • Red wine consumption was associated with increased platelet serotonin secretion after stimulation with low-dose collagen, and increased platelet aggregation at the higher collagen concentration. Red wine was, however, not associated with changes in platelet aggregation or serotonin secretion after stimulation with either sodium arachidonate or epinephrine
8	Mann et al[63]; a 3 × 3-week cross-over study: 1-week vegetarian run-in followed by 2-week meat (red, white or fish) consumption	29 healthy participants (14 men, 15 women); age, 22–52 y	3 × 3-week interventions: Week 1 = vegetarian diet followed by 2 weeks of either red meat (mean [SD], 351 [104] g/day, fat-trimmed), white meat (mean [SD], 231 [52] g/day, fat-trimmed), or fish (mean [SD], 133 [32] g/day, Atlantic salmon). This was followed by a 3-week washout period. During the next 2 cycles the meat sources (red, white or fish) were altered so all participants received all 3 treatments.	• Thrombin and collagen-induced platelet aggregation using platelet-adjusted plasma (220×10^9 platelets/l). • Platelet TXB2 production	• Increased collagen-stimulated platelet aggregation was observed following the 1-week vegetarian diet compared to baseline. • Neither white nor red meat diets affected platelet aggregation, or ex vivo platelet TXB2 production. • The fish diet had no effects on platelet aggregation, but significantly decreased collagen-stimulated platelet TXB2 production.
9	Makarewicz-Wujec et al[64]; a 6-month randomized, placebo-controlled study (Dietary Intervention to Stop Coronary Atherosclerosis in Computed Tomography)	81 participants with stable CAD: • 41 DASH (28 men, 13 women; mean age, 59 y) • 40 control group (22 men, 18 women; mean age, 60.3 y)	• DASH (high intake of fruit, vegetables, whole grains, poultry, fish, nuts and restricted saturated fat, red meat, sweet beverages and refined grains) • Control group: no dietary intervention	Plasma CXCL4	The DASH diet decreased CXCL4 concentrations among patients with stable CAD. CXCL4 also correlated negatively with vegetable intake.
10	Yazici et al[65]; a 20-week parallel study	• 36 newly diagnosed prehypertensive patients • 21 control participants (matched for age and sex). Participants did not exercise regularly.	• DASH diet and physical activity (180 min/wk, moderate intensity). • Only the prehypertensive patients underwent the intervention.	• Mean platelet volume • Platelet count • Platelet mass	Mean platelet volume was significantly decreased following the DASH and exercise intervention in the prehypertensive group, signifying decreased platelet activation.

Abbreviations: ADP, adenosine diphosphate; AMI, acute myocardial infarction; CAD, coronary artery disease; CXCL4, platelet factor 4; DASH, Dietary Approaches to Stop Hypertension; HFD, high-fat diet; MD, Mediterranean diet; TXB2, thromboxane B2

TABLE 3 Factor VII and plant-based diets (continued on the next page)

No.	Author	Study population	Type of diet	Biomarker	Main results
Cross-sectional					
1	Mezzano et al[43]	54 participants with no comorbidities: •26 vegetarians (12 men, 14 women) = 3 vegans and 23 lacto-vegetarians/lacto-ovo-vegetarians (mean age, 39 y) •26 omnivores (age-, sex-, and socioeconomic status–matched); Chile	•Vegetarian (vegan and lacto-vegetarian/lacto-ovo-vegetarian) •Omnivore (higher SFA intakes compared to vegetarian diet) • >1 year on diet	FVIIc	FVIIc was significantly lower in the vegetarian group compared with omnivores.
2	Pan et al[46]	114 participants with no comorbidities: •55 Buddhist vegetarians (23 men, 32 women) •59 omnivores (20 men, 39 women) Age, 20–30 y; Chinese participants	•Vegetarian (no fish or meat) •Omnivore (higher SFA intakes compared to vegetarian diet) • >2 years on the diet	FVIIc	No significant difference in FVIIc between vegetarians and omnivores.
3	Li et al[49]	139 healthy men; age, 20–50 y: •18 vegans •43 lacto-ovo-vegetarians •60 moderate meat-eaters •18 high meat-eaters; nonsmoking	•Habitual intakes (at least 6 months prior to study) •Vegans •Lacto-ovo-vegetarian •Moderate meat-eater (<285 g/day) •High meat-eater (>285 g/day) (Higher SFA intakes in meat-eaters)	FVIIact (ACL 200 system)	Vegans had a significantly lower FVIIact than meat-eaters
4	Mia and Vorster[48]	321 Indian adolescents: •31 lacto-ovo-vegetarian (11 men, 20 women) •290 omnivores (148 men, 142 women) Age, 16–18 y; South Africa	•Lacto-ovo-vegetarian •Omnivore •Indian vegetarian diet was not lower in fat (>40% TE in both groups) or higher in fiber than the omnivore diet.	FVIIc	FVIIc did not differ between the lacto-ovo-vegetarian and omnivore groups. The number of vegetarians in this study was small (10%) and the results therefore cannot be extrapolated to the general vegetarian population.
5	Haines et al[50]; controls were from the Northwick Park Heart Study	332 non-smokers, not using oral contraception; age, 18–65 y: •282 omnivores (211 men, 71 women) •50 vegetarians (27 vegan, 23 lacto-ovo-vegetarian; 25 men, 25 women)	•Vegetarian (vegan and lacto-ovo-vegetarian) •Omnivore	FVII (%)	FVII was significantly lower in the vegetarians compared to the omnivores.
Intervention					
6	Marckmann et al[56]; a randomized cross-over study with intervention duration of 2 weeks and a 2-to-6-week washout period	20 healthy women; age, 21–52 y; BMI, 20–25 kg/m^2	3 ad libitum experimental diets: •A diet rich in starchy foods (STARCH), composed according to the Nordic Nutrition Recommendations: <30 %E total fat;<10 %E saturated fatty acids; and >3 g/MJ fiber •A sucrose-rich diet (SUCROSE), resembling the STARCH diet except for the inclusion of additional sucrose (approximately +20 E%, or 120 g sucrose per 10 MJ) in the place of starchy foods (primarily bread, rice, pasta, and cereals). •And a high-fat diet (FAT) that had a fat content of 45 to 50 E% and a dominance of saturated fatty acids. •The experimental diets were identical with respect to fish and marine n-3 polyunsaturated fatty acid content.	FVIIc	Nonfasting FVIIc was significantly lower following the starch (Nordic) diet compared to the sucrose or fat diets, with nonfasting FVIIc levels also lower in the starch group; however, not significantly so.

TABLE 3 Factor VII and plant-based diets (continued from the previous page)

No.	Author	Study population	Type of diet	Biomarker	Main results
7	Marckmann et al[57]; a randomized, crossover, 2-week study	21 healthy middle-aged individuals: • 11 women (5 postmenopausal; mean age, 52 y) • 10 men (mean age, 53 y) 5 light smokers; Denmark	• Nordic nutrition recommendations: low-fat (28% of energy), high fiber (3.3 g/MJ). Larger amounts of fish, bread and cereals, vegetables and fruit. Energy, 10.4 MJ • Average Danish diet (Dane diet): high-fat diet (39% energy), low-fiber. Energy, 10.5 MJ	• FVIIc (one-stage clotting assay) • FVIIag • FVIIc to FVIIag ratio	• The Nordic diet lowered plasma FVIIc significantly while FVIIag and the FVIIc to FVIIag ratio were virtually unaffected by the dietary change. • A low-fat, high-fiber diet reduced the thrombogenic tendency compared to a diet corresponding to the average Danish diet.

Abbreviations: FVIIact, factor VII activity; FVIIag, factor VII antigen; FVIIc, factor VII coagulant activity; SFA, saturated fatty acid; TE, total energy; others, see TABLE 1

individuals in poor health, but not in healthy individuals.[70] This is in agreement with a recent review by Siniarski and Gajos[75] that a degree of uncertainty still remains regarding the use of polyunsaturated fatty acids in the prevention of CVD since the initial promising findings from intervention studies were not supported by recent meta-analyses and differences in the approach of seminal clinical trials resulted in divergent results. Furthermore, plant-based n-3 fatty acids were found to be less effective inhibitors of platelet aggregation than fish oils.[76]

Lastly, plant-based diets are a source of dietary salicylic acid. It has previously been reported that vegetarians can have serum salicylic acid levels as high as patients taking 75 mg of aspirin a day.[77] In fact, Janossy et al[78] reported that a variety of plant foods can exert effects on platelet function comparable to those of prescription medicine and as such, dietary intake may need to be considered when prescribing antithrombotic (aspirin) treatment. This is in agreement with the recommendation by Aimo and De Caterina[79] that aspirin treatment for primary prevention of CVD should be based on a tailored approach that considers the combined assessment of thromboembolic and bleeding risk, the patient's general health, general preventive measures (that can include a plant-based diet), and the patient's 10-year CVD risk.

Plant-based diets and factor VII Although there is some evidence for the effect of plant-based diets on FVII, less information is available than for fibrinogen and platelets. We found 5 cross-sectional studies of which 3 report decreased FVII (measured as FVII coagulant activity [FVIIc], FVII activity, and percentage) in vegans and lacto-ovo-vegetarians compared with omnivores[43,49,50] and 2 report no differences (FVIIc)[46,48] (TABLE 3). Two intervention studies,[56,57] each with a duration of 2 weeks, investigating the Nordic diet, found lower FVIIc compared with the respective control diets while in one, no effect was observed for FVII antigen (FVIIag) or the FVIIc to FVIIag ratio.[57] Diet-related factors that have been associated with higher FVII include obesity (reviewed by Pieters and De Maat[11]) and consumption of saturated fatty acids, particularly C12–C16[80,81] which tend to be lower in plant-based consumers. The mechanism whereby dietary fat leads to FVII activation remains uncertain. Possible explanations include association with triglyceride-rich lipoproteins, chylomicron size, serum phospholipid concentration, and the presence of procoagulant aminophospholipids as minor components of lipoproteins.[82,83] Another novel proposal is that FVII activation follows the shift of pro-coagulant phospholipids such as phosphatidylserine from the inner to the outer leaflet of cell-surface membranes.[84] Alcohol[85] and fiber consumption,[57,86] on the other hand, have been demonstrated to decrease FVII. According to a review by Lee and Lip,[87] there is no consistent effect of n-3 supplementation on FVII, with the majority of the studies finding no effect. Taken together, these data could suggest that the lower FVIIc observed in the studies employing the Nordic diet may not be the result of active lowering of FVII by the diet, but by higher levels in the control diets which were both high in fat. In agreement with this, none of vegetarian participants in any of the cross-sectional studies listed above that reported lower FVII levels consumed fish, while 3 of the 5 studies reported the control groups to consume higher amounts of saturated fats,[43,46,49] with one study[50] not reporting fat intake. Lastly, the study by Mia and Vorster[48] that found no difference in FVII between vegetarians and omnivores explicitly stated that there was no difference in total fat or fiber intake between the 2 groups.

Plant-based diets and fibrinolysis There were 11 studies that investigated the association between plant-based diets and fibrinolysis, measured either as concentration or activity of individual proteins in the lytic pathway (activators and inhibitors) or making use of global assays (TABLE 4). Four of the 7 cross-sectional studies found no

TABLE 4 Fibrinolysis and plant-based diets (continued on the next page)

No.	Author	Study population	Type of diet	Biomarker	Main results
Cross-sectional					
1	Famodu et al[42]; selection based on habitual intakes	76 participants with no comorbidities; mean age, 48 y: • 8 vegans (mean age, 47.1 y) • 28 lacto-ovo-vegetarians (mean age, 49 y) • 40 ominovers (age- and BMI-matched) Nigeria	• Vegan • Lacto-ovo-vegetarian • Omnivore (habitual African diet)	• ELT (modified Von Kaulla method)	• ELT was significantly shorter in the lacto-ovo--vegetarian and vegan groups compared with the omnivores thus indicating higher fibrinolytic activity. • ELT was also significantly shorter (thus higher fibrinolytic activity) in the lacto-ovo-vegetarian compared with the vegan group.
2	Mezzano et al[43]	54 participants with no comorbidities: • 26 vegetarians (12 men, 14 women) = 3 vegans and 23 lacto-vegetarians / lacto-ovo--vegetarians (mean age, 39 y) • 26 omnivores (age-, sex-, and socioeconomic status–matched) Chile	• Vegetarian (vegan and lacto-vegetarian / lacto-ovo--vegetarian) • Omnivore • >1 year on diet	• tPAag • PAI-1ag • Plasminogen • PAP	• Plasminogen was significantly lower in the vegetarian compared with the omnivore group. • PAP, tPAag and PAI-1ag showed no significant difference between the groups.
3	Pan et al[46]	114 Chinese participants with no comorbidities: • 55 Buddhist vegetarians (23 men, 32 women) • 59 Omnivores (20 men, 39 women) Age, 20–30 y	• Vegetarian (no fish or meat) • Omnivore • >2 years on the diet	Plasminogen	No significant difference in plasminogen between vegetarians and omnivores.
4	Liese et al[45]; the Insulin Resistance Atherosclerosis Study	880 middle-aged adults, 144 with diabetes mellitus; age, 45–74 y; African American, Hispanic, and non-Hispanic White participants; USA	Identification of food patterns associated with fibrinogen using reduced rank regression	PAI-1ag (2-site immunoassay sensitive to free active and latent PAI but not PAI-1 complexed with tPA)	PAI-1 had a positive association with the food pattern containing high intake of red meat, low--fiber bread and cereal, dried beans, fried potatoes, tomato vegetables, eggs, cheese and cottage cheese and low intake of wine.
5	Ho and Chwang[88]	35 healthy participants: • 15 vegetarian (lacto--vegetarian and lacto-ovo--vegetarian; 3 men, 12 women; mean age, 46.2 y) • 20 omnivores (6 men, 14 women; mean age; 38.3 y)	• Vegetarian (12 consumed milk, 14 consumed eggs) • Omnivore	• tPAag • PAI-1act • ELT Before and after venous occlusion test	There was no significant difference in tPAag, PAI--1act or ELT before or after the venous occlusion test between the vegetarians and omnivores.
6	Li et al[49]	139 healthy men; age, 20–50 y: • 18 vegan • 43 lacto-ovo-vegetarian • 60 moderate meat-eaters • 18 high meat-eaters; nonsmoking	• Habitual intakes (at least 6 months prior to study) • Vegan • Lacto-ovo-vegetarian • Moderate meat-eater (<285 g/day) • High meat-eater (>285 g/day)	Plasminogen	Plasminogen did not differ significantly between the 4 dietary groups.
7	Haines et al[50]; controls were from the Northwick Park Heart Study	332 non-smokers, not using oral contraception; age, 18–65 y: • 282 omnivores (211 men, 71 women) • 50 vegetarians (27 vegan, 23 lacto-ovo-vegetarian; 25 men, 25 women)	• Vegetarian (vegan and lacto-ovo-vegetarian) • Omnivore	Fibrinolytic activity (method of Fearnley and Chakrabarti expressed as the reciprocal of blood clot lysis time in hours × 100)	Fibrinolytic activity was significantly lower in vegetarian men than in omnivorous men.

TABLE 4 Fibrinolysis and plant-based diets (continued from the previous page)

No.	Author	Study population	Type of diet	Biomarker	Main results
Intervention					
8	Kim et al[91]; randomized crossover study of two 4-week interventions with a washout period of minimum 2 weeks (average, 3 weeks)	51 (15 men, 36 women) participants without type 2 diabetes; mean age, 35.1 y; Australia/New Zealand	•HMD = diet high in red (200–300 g/d) and processed meat (> 50g/d) and refined grains •HWD = diet high in whole grains, nuts, legumes and dairy. Total energy was matched, and vegetables and fruit were limited to 1–2 servings in both diets.	PAI-1ag	•PAI-1ag was higher after the HMD than after the HWD. •There was a strong linear inverse association between PAI-1ag and whole grain intake in the HWD diet group.
9	Lopez-Learrea et al[90]; an 8-week randomized, parallel trial (RESMENA: Metabolic Syndrome Reduction in Navarra)	96 Caucasian participants (51 men, 45 women) with obesity and metabolic syndrome features; mean age, 50 y: •48 RESMENA •46 AHA; Spain	•RESMENA diet (–30% energy, 30% energy from protein = higher total protein, significantly more meat--derived protein) •Control diet: AHA diet (–30% energy, 15% energy from protein = lower total protein, significantly less meat-derived protein). Both groups had similar intakes of vegetable and fish proteins.	PAI-1ag	PAI-1ag was significantly reduced in the control--diet, and only borderline significantly decreased in the RESEMNA (high protein) diet following the 8-week intervention.
10	Erlinger et al[89]; a 4-week parallel intervention	55 hypertensive participants (35 African-American, 20 Whites) taking no anti--hypertensive medication/agreed to undergo supervised withdrawal of antihypertensive medication for 2 weeks prior to screening: •27 DASH •28 control	•DASH diet •Control diet The DASH diet was lower in total and saturated fats and higher in fruit, vegetables and low-fat dairy products. Diets did not differ regarding sodium content (approximately 3 g/day).	•tPAag •tPAact •PAI-1act	The DASH diet did not affect any of the fibrinolytic markers.
11	Marckmann et al[57]; a 2-week randomized, crossover study	21 healthy middle-aged individuals: •11 women (5 postmenopausal; mean age, 52 y) •10 men (mean age, 53 y) 5 light smokers; Denmark	•Nordic nutrition recommendations: low-fat (28% of energy), high fiber (3.3 g/MJ). Larger amounts of fish, bread and cereals, vegetables and fruit. Energy, 10.4 MJ •Average Danish diet (Dane diet): high-fat diet (39% energy), low-fiber. Energy, 10.5 MJ	•EFA •tPAag •tPAact •PAI-1ag •PAI-1act	•The Nordic diet increased fibrinolytic activity: EFA, tPAact and t-PA:PAI-1 ratio were increased following the Nordic diet while the Danish diet resulted in decreased levels. •tPAag, PAI-1ag and PAI-1act were not affected by either diet.

Abbreviations: AHA, American Heart Association; EFA, euglobulin fibrinolytic activity; ELT, euglobulin lysis test; PAI-1, plasminogen activator inhibitor-1; PAI-1ag, plasminogen activator inhibitor-1 antigen; PAP, plasmin-antiplasmin complex; tPA, tissue plasminogen activator; tPAact, tissue plasminogen activity; tPAag, tissue plasminogen activator antigen; others, see **TABLE 2**

difference in fibrinolytic markers between vegetarians (vegans and lacto-ovo-vegetarians) and omnivores.[43,46,49,88] One reported higher fibrinolytic activity,[42] one decreased fibrinolytic activity,[50] and another lower plasminogen levels.[43] One study reported a positive association between plasminogen activator inhibitor-1 (PAI-1) and a dietary pattern containing red meat, low--fiber bread, and dairy.[45] Regarding intervention studies, a study comparing a 4-week DASH diet to a control diet higher in total and saturated fats and lower in fruit, vegetables, and low-fat dairy, found the DASH diet to have no effect on any of the fibrinolytic markers analyzed.[89] A 2-week Nordic diet, compared with a high-fat Danish diet, resulted in increased fibrinolytic activity (euglobulin lysis test) and increased tissue plasminogen activator activity but had no effect on PAI-1.[57] Two studies comparing an 8-week American Heart Association diet[90] and a 4-week diet high in whole grains, nuts, legumes, and dairy[91] with diets high in meat, both found PAI-1 antigen to be higher in meat-consumers. Kim et al[91] additionally reported an inverse association between PAI-1 and whole grain intake.

The evidence for dietary factors that can improve fibrinolysis is limited and inconclusive. Nutrients and foods that have, thus far, received the most attention include alcohol, fats (monounsaturated fatty acids, n-3 fatty acid supplementation), and a number of micronutrients such as vitamin C, D, and E, retinol, and zinc (reviewed

TABLE 5 Other hemostatic factors and plant-based diets (continued on the next page)

No.	Author	Study population	Type of diet	Biomarker	Main results
Cross-sectional					
1	Pan et al[46]	114 participants with no comorbidities: • 55 Buddhist vegetarians (23 men, 32 women) • 59 omnivores (20 men, 39 women); Age, 20–30 y; Chinese participants	• Vegetarian (no fish or meat) • Omnivore • >2 years on the diet	• PT • APTT • FVIIIc • ATIII	• There was no significant difference in PT between the vegetarian and omnivore groups. • Vegetarian men had significantly higher concentrations of ATIII than omnivorous men. • Vegetarian women had significantly higher FVIIIc and shorter APTT than omnivorous women.
2	Mezzano et al[43]	54 participants with no comorbidities: • 26 vegetarians (12 men, 14 women) = 3 vegan and 23 lacto-vegetarian/lacto-ovo--vegetarian (mean age, 39 y) • 26 Omnivores (age-, sex-, and socioeconomic status–matched); Chile	• Vegetarian (vegan and lacto-vegetarian/lacto-ovo--vegetarian) • Omnivore • >1 year on diet	• APTT • TT • PT • vWF • FVIIIc • FVc • TAT • Prothrombin • ATIII • Protein C • Total Protein S • Fibrin degradation products	• Plasma levels of all coagulation or fibrinolytic factors and natural inhibitors synthesized in the liver were lower in vegetarians than in omnivorous controls. For hemostatic proteins of predominantly extrahepatic origin this tendency was not present. • ATIII and total Protein S were significantly lower in the vegetarian group compared to omnivorous controls. • PT was borderline significantly longer and prothrombin borderline significantly lower in the vegetarian group compared to the omnivorous controls. • APTT, thrombin time, vWF, FVIIIc, FVc, TAT, Protein C, fibrin degradation products did not differ between the groups.
3	Haines et al[50]; controls were from the Northwick Park Heart Study	332 non-smokers, not using oral contraception; age, 18–65 y: • 282 omnivores (211 men, 71 women) • 50 vegetarians (27 vegan, 23 lacto-ovo-vegetarian; 25 men, 25 women)	• Vegetarian (vegan and lacto-ovo-vegetarian) • Omnivore	• FV • FVIII • FII • FX • ATIII (biological) • ATIII (immunological)	• There was no difference in FV, FVIII, FX, or ATIII (biological) between vegetarians and omnivores. • FII and ATIII (immunological) were significantly lower in vegetarian men than omnivorous men.
4	Li et al[49]	139 healthy men; age, 20–50 y: • 18 vegans • 43 lacto-ovo-vegetarians • 60 moderate meat-eaters • 18 high meat-eaters; nonsmoking	• Habitual intakes (at least 6 months prior to study) • Vegan • Lacto-ovo-vegetarian • Moderate meat-eater (<285 g/day) • High meat-eater (>285 g/day)	• PT (INR) • APTT • ATIII	No significant difference between the 4 dietary groups for PT, APTT or ATIII.
5	Suwannuruks et al[47]	80 participants: • 30 vegans (15 men, 15 women) • 10 lacto-vegetarians • 10 lacto-ovo-vegetarians • 30 omnivores (not matched; 15 men, 15 women) No comorbidities; age, 18–50 y; Thailand	• Vegetarian (vegan, lacto--vegetarian, lacto-ovo--vegetarian) • Omnivore • >4 years on diet	• APTT • PT • TT	No significant difference in APTT, PT and TT between the vegetarians and omnivores.

TABLE 5 Other hemostatic factors and plant-based diets (continued from the previous page)

No.	Author	Study population	Type of diet	Biomarker	Main results
Intervention					
6	Mezzano et al[62]; a 90-day intervention	42 healthy men (mean age, 22 y): •21 MD •21 HFD Chile	•Alcohol-free MD •HFD •Fats supplied 27.3 and 39.9% of energy in the MD and HFD, respectively. •White meat, fish and legumes were the main source of proteins in the MD, whereas the HFD was rich in red meat and low in fish. •Both diets were isoenergetically supplemented with 240 ml/day red wine from day 31–60.	•Forearm bleeding time •vWFag	•The MD group had significantly longer bleeding times than the HFD after 30 days. There was no significant difference in vWFag. •Red wine consumption did not significantly alter bleeding time or vWFag.

Abbreviations: APTT, activated partial thromboplastin clotting time; ATIII, antithrombin III; FII, factor II; FVc, factor V coagulant activity; FX, factor X; PT, prothrombin time; TAT, thrombin-antithrombin complex; TT, thrombin time; vWF, von Willebrand factor; vWFag, von Willebrand factor antigen; others, see TABLES 2 and 3

by Lee and Lip[87] and Pieters and De Maat[11]). For most of these, the number of investigations is limited, and the available evidence produced contradictory findings. Also, most of the studies investigated individual activators or inhibitors in the fibrinolytic pathway such as plasminogen, or tissue plasminogen activator or PAI-1 activity or antigen as surrogate markers of fibrinolytic activity, without directly measuring fibrinolytic potential.

The evidence for dietary habits that can inhibit fibrinolysis is much stronger. Again, for individual nutrients and foods, the evidence is limited, but there is a strong relationship between consequences of overnutrition such as obesity and metabolic syndrome and decreased fibrinolytic potential and in particular increased PAI-1. A major source of PAI-1 is adipose tissue, with visceral fat producing more PAI-1 than subcutaneous fat, since it produces more proinflammatory cytokines, which stimulates PAI-1 secretion (being an acute-phase protein) and it contains more stromal cells, which is the cellular component of adipose tissue that produces PAI-1.[92-94] The metabolic syndrome is characterized by abdominal obesity, as well as dyslipidemia, hypertension, and glucose intolerance (insulin resistance), all of which have been linked to increased PAI-1.[95,96] In fact, the relationship of PAI-1 with metabolic syndrome is so strong, that it is considered by some to be a true component of the metabolic syndrome.[97] In agreement with PAI-1, global fibrinolytic assays have also demonstrated decreased lysis in both obesity and metabolic syndrome, confirming their hypofibrinolytic effects.[98,99]

Thus, while the evidence for the effect of individual components of plant-based diets on fibrinolysis is still to be confirmed, the lower prevalence of obesity[7] and metabolic syndrome in plant-based consumers (reviewed by Babio et al[100])supports a beneficial relationship between plant-based diets and fibrinolytic potential.

Plant-based diets and other hemostatic factors The relationship between plant-based diets and a number of other hemostatic variables have also been investigated and is summarized in TABLE 5, although the number of studies is small with varying results. Five cross-sectional studies[43,46,47,49,50] found no difference in some, but not all of the hemostatic variables measured between vegetarians (vegans and lacto-ovo-vegetarians) and omnivores, and 3[43,46,50] reported both lower levels of some and higher levels of other hemostatic variables in vegetarians. There was one intervention study of 90 days that reported longer bleeding times following a Mediterranean diet but no difference in von Willebrand factor levels compared with a high-fat diet.[62] The addition of wine did not significantly affect either outcome. Mezzano et al[43] concluded that these findings may be related to the origin of the hemostatic factors since plasma levels of coagulation or fibrinolytic factors and inhibitors synthesized in the liver were lower in vegetarians than in omnivorous controls while those of predominantly extrahepatic origin were not. Much more research, in particular large intervention trials, is required to corroborate findings regarding the effect of plant-based diets on these hemostatic variables, before firm conclusions can be drawn or recommendations to the public can be made.

Conclusion Healthy plant-based diets have established benefits for cardiometabolic health, and they may do so, in part, through effects on thrombotic factors. However, this relationship is complex and depends on the energy, nutrient, and food composition of the diet. Strictly vegan diets, if not carefully planned and balanced may result in deficiencies (eg, n-3 fatty acids and vitamin B_{12}) that may have a negative impact on thrombosis. While some components of plant-based diets (eg, fiber, phytochemicals, long-chain n-3 polyunsaturated fatty acids, moderate alcohol consumption) may actively decrease thrombotic factors, the limiting of prothrombotic components (eg, saturated fat and animal protein), present in typical omnivorous diets, may provide indirect benefit. In addition, healthy plant-based diets, being comparatively hypo-caloric (regardless of the composition), generally protect against overnutrition and its metabolic consequences such as obesity and metabolic syndrome, which are also considered prothrombotic. A one-size-fits-all conclusion can therefore not be drawn as the potential antithrombotic effect of different plant-based diets depends on the nutrient composition (based on the degree of exclusion of animal products), the content of active antithrombotic dietary components, the relative absence of prothrombotic dietary factors as well as the degree of total caloric restriction.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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