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The impact of PBD (plant-based diet) on atherosclerosis biomarkers in the risk and progression of coronary heart disease: A systematic review of randomized controlled trials

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ABSTRACT

Background: Coronary heart disease (CHD) is a leading cause of premature death globally. Plant-based diet (PBD), which emphasizes vegetables, fruits, legumes, grains, oils, and nuts with minimal animal products, is gaining attention for its potential cardiovascular benefits. It may impact atherosclerosis progression by improving lipid profiles, inflammation, blood pressure, and endothelial function.

Objective: This review evaluates the effects of PBD on atherosclerosis biomarkers in at-risk individuals and CHD patients.

Methods: A systematic review of randomized controlled trials (RCTs) published between 2019 and 2024 was conducted using keywords: "Plant based diet" OR "Mediterranean diet" OR "Vegan diet" OR "Diet" AND "Atherosclerosis". Studies included were focused on the impact of PBD on blood lipid profile, inflammatory markers, measurements of atherosclerosis progression, anthropometrics, and blood pressure in populations with or without CHD. Databases searched included Cochrane, ScienceDirect, PubMed, Scopus, ProQuest, JSTOR, and ACM.

Results: Sixteen out of 2960 studies were reviewed, involving 5,408 participants with interventions ranging from 4 weeks to 7 years. PBD was found to significantly improve lipid profiles by lowering total cholesterol, low-density lipoprotein (LDL), and triglycerides. PBD also reduced inflammatory markers (C-reactive protein (CRP), interleukins), improved endothelial function, and arterial stiffness measurements. It also reduces body weight, waist circumference, and blood pressure. This review highlights the potential of PBD to mitigate cardiovascular risk through improvements in lipid metabolism, inflammation, and endothelial function. While some outcomes varied, evidence supports the incorporation of PBD as a strategy to slow the progression of atherosclerosis to improve cardiovascular health.

Conclusion: PBD was found to improve atherosclerosis biomarkers in at-risk individuals and CHD patients by reducing inflammation and improving lipid profiles. Future studies should further explore these relationships, especially on arterial stiffness with larger populations and homogenous sample sizes to establish robust conclusions.

Keywords: Atherosclerosis progression; blood lipid profile; coronary heart disease; inflammatory markers; plant-based diet

BACKGROUND

The term plant-based diet (PBD) primarily focuses on the consumption of plant-based foods including vegetables and fruits, legumes, grains, oils, nuts, seeds, with minimal inclusion of animal products like milk, eggs, meat, and fish.[1] Vegetarianism prevalence differ globally, with approximately 5% of Americans, 8% of Canadians, 4.3% of Germans, and nearly 30% in India.[2] In the Asia-Pacific region, although 19% of the population identify as vegetarian, only 5% actually adhere to a vegetarian diet.[3] However, interest in plant-based food in Indonesia is growing rapidly. According to The Global Vegetarian Index, Indonesia is one of the best countries for vegetarian food. Based on Indonesia Vegetarian Society data in 2023, approximately 2 million people adopt vegetarian as their lifestyle. Additionally, 90% of Indonesians are now trying to consume healthier foods to boost immunity.[4]

Plant-based diet (PBD) is known to offer protective effects in the prevention and treatment against metabolic diseases.[5] A previous review summarized various PBD effect in improving risk markers for cardiometabolic diseases, such as body weight, lipid profile, and others.[6] PBD have significantly lower plasma cholesterol levels, mainly due to the avoidance of meat and, in the case of vegans, dairy products as well. Plant-based foods such as nuts and seeds are rich in polyunsaturated fatty acids, fiber, and sterols, which can

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help lower cholesterol levels by reducing its absorption in the intestine and increasing LDL uptake by the liver. Substituting saturated fats with monounsaturated and polyunsaturated fats can reduce the risk of coronary heart disease (CHD) up to 25%. Additionally, a PBD containing vegetables, whole grains, nuts, and fruits provides vitamins, minerals, and phytochemicals with antioxidant properties such as tannins, phenols, alkaloids, and flavonoids that help prevent atherosclerosis by reducing lipoprotein oxidation, improving endothelial function, and regulating immune responses.[7]

The Lifestyle Heart Trial showed that PBD improved atherosclerosis by about 34% higher than the standard American Heart Association diet.[8] Atherosclerosis is the primary mechanism of the development of vascular diseases such as coronary heart disease. Low-grade chronic inflammation triggered by lipid accumulation leads to endothelial injury and lipid infiltration. This process promotes foam cell formation through macrophage adherence and drives plaque development via continuous release of pro-inflammatory cytokines (TNF-α, IL-1, IL-6, and MCP-1) within the vessel wall, resulting in either obstructive or non-obstructive atherosclerotic plaques.[9,10] In short, the elevation of low-density lipoprotein (LDL) levels contributes to its deposition beneath the endothelium, while inflammatory mediators exacerbate disease progression.[11,12] A healthy diet with anti-inflammatory effects can help improve systemic inflammation, which in turn may lower the risk of chronic diseases development and reduce overall mortality.[13]

There are a lot of primary studies and reviews examining the positive relationship between PBD and CHD. However, evidence regarding the cardioprotective or mortality-reducing effects of PBD in CHD remains inconsistent, mainly due to different diet quality and other lifestyle habits (physical activity, smoking, alcohol use).[7] This review aims to summarize newer findings to present more concise data on the effectiveness of PBD in improving the progression of atherosclerosis biomarkers in patients with CHD and at-risk populations.

METHODS

Eligibility criteria

Inclusion criteria were: (1) true experimental studies (RCT) on PBD in healthy population or with coronary heart disease, with minimal intervention period of 4 weeks; (2) study published in English for the last six years (2019–2024); (3) studies with participants of age $\geq$ 18 years. Our definition of PBD consists of minimally processed foods (vegetables, fruits, grains, nuts, legumes, spices, etc), may or may not include limited amount of animal-based foods (eggs, dairy, fish, meat) and additional supplementation (e.g. extra virgin olive oil, nuts). Observational studies and study on animals were excluded to ensure the homogeneity of the results.

Search strategy

Selection of study articles was done by four independent researchers. The search was conducted using electronic databases (Cochrane, ScienceDirect, Pubmed, Scopus, Proquest, JSTOR, ACM) using different combinations of specific terms: "Plant based diet" OR "Mediterranean diet" OR "Vegan diet" OR "Diet" AND "Atherosclerosis".

Data collection

Article collection, identification, and screening were done using Rayyan AI. Important results from selected articles were extracted and tabulated in Microsoft Excel and grouped based on biomarkers that contribute to the initiation process (blood lipid profile, inflammatory markers), structural and functional vascular changes caused by atherosclerosis progression, and risk factors that accelerate atherosclerosis development (anthropometric measure, blood pressure). Other results deemed necessary to support the research were also included.

Study selection

A total of 2960 articles were identified in the database search. After 509 duplicate articles were removed, 2451 articles were screened. An extensive exclusion of 2000 articles were carried out as they did not align with the specific topic of interest. This was partly due to the use of broad search keywords, which resulted in the retrieval of studies outside the intended scope. Two additional articles were found in the manual search. Then, 44 articles were evaluated. After eliminating study articles that did not fit the inclusion criteria, 16 studies were selected and inserted in this systematic review. A comprehensive explanation of the study selection can be seen in Figure 1.

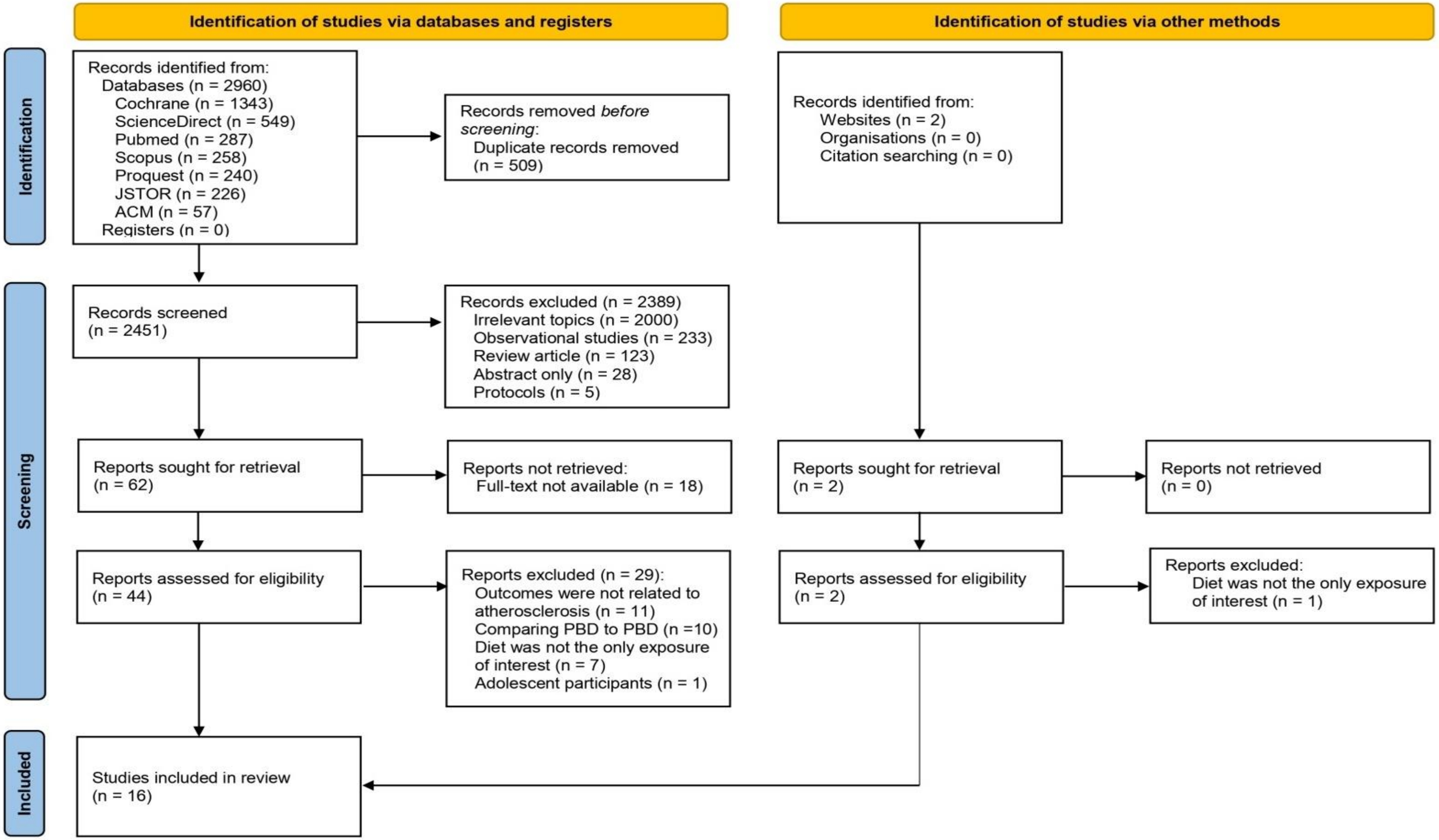


Figure 1. PRISMA Flowchart For Study Selection

RESULT

Study characteristics

The studies included were published between 2019 and 2024. The studies were conducted in various countries, nine studies in Mediterranean countries (Spain, Italy, France, and Israel), six in other countries (USA, Sweden, Australia, and Singapore), and one conducted across five countries at once (Italy, England, the Netherlands, Poland, and France). All study designs were Randomized Controlled Trials (RCTs). The total number of participants included in this systematic review was 5408 people consisting of 2439 patients with a history of CHD, 1564 participants with risks of cardiovascular disease, and 1405 healthy participants. All studies included both men and women, except for two studies that did not report gender (Table 1).

The intervention was PBD with intervention period ranging from 4 weeks to 7 years.[14,15] All studies compared PBD with meat-containing diet. A total of 11 studies reported Mediterranean diet interventions (either with the extra virgin olive oil, mixed nuts, or green-Mediterranean diet), three studies conducted intervention with vegan diet, and two studies with plant-based alternative/analogue meat diet. All studies assessed outcomes related to the risk and progression of atherosclerosis.

There were 14 parallel studies and two cross-over studies included in this systematic review. The risk of bias lies in the randomization process. None of the participants in the included RCTs were blinded. The assessors and laboratory technicians in 10 studies were blinded to the intervention received by the participants, the remaining six studies did not provide details. Furthermore, participants' adherence to dietary interventions in most studies was assessed through self-report and questionnaires, which may lead to under- or overestimation of dietary intake. In cross-over studies, the risk of bias lies in the presence and absence of a washout period. Of the two cross-over studies included, only one reported a washout period. The report of a washout period could help identify significant intervention sequence effects.[16]

Effects of PBD on blood lipid profiles

A total of six studies reported total cholesterol value, all of them demonstrated a lower total cholesterol level following PBD intervention, but only three showed a significant result.[14,17,18] Nine studies report the results of Low-Density Lipoprotein (LDL) measurement, all suggested that PBD can reduce LDL levels, but only six showed significant reductions. [14,16–20] No significant changes of LDL were found in control group (Table 1).

Nine studies reported the results of High-Density Lipoprotein (HDL) measurements. Overall, only five showed an increase in HDL with no significant changes, [16,17,20–22] and four showed a decrease in HDL.[14,18–20,23] Meanwhile in the control group, one study showed a decrease and one study showed an increase in HDL.[18] Similar results were found in triglyceride measurements. Only one showed a significant decrease in triglycerides, both in intervention group and control group. [18] The inconsistency of the result may be due to non-adherence to the diet style, lack of washout period, short-term study, and the impact of the COVID-19 pandemic on the delivery of dietary sources.[16,17,22,23]

Effects of PBD on inflammatory markers

In this systematic review, ten studies assessed the relationship between PBD and inflammatory markers that have a strong correlation with atherosclerosis mechanism (Table 1). Out of three studies, two showed a significant decrease of trimethylamine N-oxide (TMAO).[14,16,19] Insignificant results were found for Insulin-like Growth Factor 1 (IGF-1).[16] PBD showed a significant decrease in serum resistin values compared to the control group.[17] Out of four studies that measured C-Reactive Protein (CRP) or high-sensitive CRP (hs-CRP), only one showed a significant decrease in hs-CRP.[14,20–22]

One study showed significant improvement in atherothrombosis biomarkers.[24] These biomarkers are platelet activating factor acetyl hydrolase (PAF-AH), HDL-bound α1-antitrypsin, non-esterified fatty acids (NEFA), antithrombin levels, d-dimer, platelet factor-4 concentrations, and prothrombin fragment 1+2 levels. Two studies assessed proinflammatory cytokines such as Interleukins1β (IL-1β), Interleukin 6 (IL-6), Interleukin 8 (IL-8), Interleukin 16 (IL-16), Interleukin 18 (IL-18), and Tumor Necrosis Factor-α (TNF-α). Both showed significant results after PBD intervention.[18,25]

Effect of PBD on atherosclerosis progression

The progression of atherosclerosis can also be assessed from the intima-media thickness of the common carotid arteries (IMT-CC), endothelial function and arterial stiffness (Table 1). The evaluation of endothelial function can be done through the measurement of reactive hyperaemia index (RHI), augmentation index (AIX), flow-mediated dilation (FMD), and laser-doppler flowmetry (LDF) to assess basal flow (BF) and reactive hyperaemia area (RHA). While pulse wave velocity (PWV) is an examination performed to assess arterial stiffness.[15,17,26–29]

Six studies assessed the relationship between PBD and atherosclerosis progression. Mediterranean diet intervention significantly reduced IMT-CC values after 5 and 7 years follow-up and reduced carotid plaque height compared to baseline.[15] Daidone's study showed a significant increase in RHI values, but no significant change in AIX.[17] Meanwhile, Jennings's study found an improvement in AIX.[29] Two studies on FMD examination found a notable increase in FMD in the PBD compared to the control group.[26,27] In BF and RHA examinations, a significant increase was obtained in the PBD group.[28] Meanwhile, in PWV measurements, no significant results were obtained in the intervention or control groups.[29]

Effects of PBD on anthropometric measures

Anthropometric examinations in this systematic review were body weight, body mass index (BMI), waist circumference, and waist-to-hip ratio (Table 1). Out of eight studies, five showed that PBD could significantly reduce body weight and BMI. A decrease in BMI of -0.21 kg/m2 ($p = 0.009$) was reported in a study by Tsaban.[20] In measuring waist circumference, the PBD group showed a greater decrease compared to control group.[20] A significant decrease in waist-to-hip ratio was also found in PBD group.[22]

Effect of PBD on blood pressure

A total of seven studies reported systolic blood pressure (SBP) and diastolic blood pressure (DBP) measurements (Table 1). Only two showed significant decrease in SBP.[20,29] Meanwhile, only one study showed significant decrease in DBP.[18]

DISCUSSION

This systematic review is the first to summarize various research findings of plant-based diet (PBD) and its impact on atherosclerosis progression in at-risk populations and patients with coronary heart disease (CHD). CHD contributed to premature mortality in men across 146 countries and in women across 98 countries. Cardiovascular diseases involve disorders of the heart and blood vessels influenced by multiple risk factors, including socioeconomic, metabolic, behavioral, and environmental.[30]

PBD is known for its potential to reduce morbidity and mortality related to CHD through mechanisms that inhibit the development and progression of atherosclerotic plaques.[24] This reduction can be evaluated through clinical and biochemical parameters, including lipid profiles, inflammatory markers, blood pressure, anthropometric parameters, and ultrasonographic assessments including measurements of arterial stiffness, carotid artery intima-media thickness, and flow-mediated dilation.[14–22]

PBD generally consist of minimally processed foods (vegetables, fruits, grains, nuts, legumes, spices, etc.). However, in some cases, these diets may include limited amounts of animal-based foods (eggs, dairy, fish, and meat).[1] Intervention group with PBD in this review also include vegetarian and Mediterranean diets, with or without additional supplementation (e.g., extra virgin olive oil, nuts). While control group consists of animal-based diets, low-fat diets (LFDs), and habitual diet.[1]

A study conducted by Urpi-Sarda demonstrated that adherence to the Mediterranean diet supplemented with extra-virgin olive oil (MedDiet-EVOO) or nuts (MedDiet-Nuts) significantly reduced low-density lipoprotein (LDL) levels and increased high-density lipoprotein (HDL) levels compared to LFD.[18] Similarly, research by Hernáez reported that these dietary interventions (MedDiet-EVOO and MedDiet-Nuts) also led to significant reductions in several atherothrombosis biomarkers, including P-selectin, platelet factor-4, fibrinogen, prothrombin fragment 1+2, antithrombin, plasminogen activator inhibitor-1 (PAI-1), and d-dimer, when compared with the LFD group.[24] Theoretically, PBD patterns have the potential to improve various atherosclerosis risk factors, including glucose metabolism, lipid profile, endothelial function, and oxidative stress. Previous studies on PBD have also demonstrated the contribution to lipid profile improvements, characterized by reductions in LDL, total cholesterol, and triglyceride levels, along with an increase in HDL concentrations.[31]

PBD is generally composed of high polyunsaturated fatty acids (PUFA) and fibers, which is essential in lowering lipid levels in individuals with dyslipidaemia. Omega-3 PUFAs obtained from fish or olive oil consumption can significantly reduce triglyceride (TG) and raise HDL levels.[32] Additionally, high intake of phytosterols found in nuts, seeds, vegetables, and fruits can also contribute to plasma cholesterol reduction through competitive absorption mechanisms in the intestines. On the other hand, polyphenol and monounsaturated fatty acid (MUFA) contained in EVOO function as chain breakers in lipid peroxidation,

Table 1. Study Characteristics

Author; Year; Journal; Country	Study design	Sample Size (M/F)	Mean age (years)	Intervention Duration	Type of Diet	Results and Conclusions				
						Lipid Profile	Inflammatory Markers	Atherosclerosis Progression	Anthropometry	Blood pressure
Crimaco A et al.; 2020; Am J Clin Nutr; USA	RCT, single blind	36 healthy participants (12/24)	50.2	8 weeks each diet phase, with no washout period	Plant-based alternative meat vs animal-based meat	LDL decreased significantly in Plant-based alternative meat compared to animal meat diet with p = 0.002. No differences were found in HDL and triglycerides.	There was a significant decrease in TMAO concentration in the Plan-based alternative meat intervention compared to the animal meat diet with p = 0.012. No significant differences were found in IGF-1.	N/A	Body weight decreased significantly during the intervention with Plant-based alternative meat (p < 0.001).	No significant differences were found in SBP and DBP.
Daidone M et al.; 2024; PLOS ONE; Italy	RCT, single blind	153 participants with high risk of cardiovascular disease (83/66)	65.6	12 months	MedDiet vs LFD	There was a significant decrease in total cholesterol levels within 6 months in the MedDiet group with p = 0.0003. There was a significant decrease in total cholesterol (p < 0.0005) and LDL (p = 0.009) levels within 12 months in the MedDiet group.	There was a decrease in serum resistin within 6 months and 12 months of follow-up with the MedDiet intervention.	There was a significant increase in RHI values at the 6th and 12th month follow-up in the MedDiet group compared to the LFD. Meanwhile, there was no significant change in AIX values in both groups.	N/A	N/A

Table 1. Study Characteristics (continue…)

Author; Year; Journal; Country	**Study design**	**Sample Size (M/F)**	**Mean age (years)**	**Intervention Duration**	**Type of Diet**	**Results and Conclusions**				
						Lipid Profile	**Inflammatory Markers**	**Atherosclerosis Progression**	**Anthropometry**	**Blood pressure**
Djekic D et al.; 2020; JAHA; Sweden	RCT	31 coronary heart disease patients (25/6)	67	4 weeks per diet phase, separated by washout period	VD vs MD	Total and LDL cholesterol decreased significantly in the VD group compared to MD ($p = 0.001$, $p = 0.02$).	There was no significant difference in hs-CRP levels between the two groups. In both VD and MD, there was a decrease in TMAO levels.	N/A	There was a significant decrease in body weight and BMI in the VD group. ($p = 0.0008$ and $p = 0.0009$)	No significant differences were found between the two groups.
Hernáez A et al.; 2020; Molecular Nutrition Food Research; Spain	RCT	358 participants with high risk of cardiovascular disease (131/227)	66.8	1 year	MedDiet-EVOO, MedDiet-Nuts vs LFD	N/A	There were improvements in atherothrombosis biomarkers with the MedDiet-EVOO and MedDiet-Nuts interventions compared with LFD.	N/A	N/A	N/A
Jennings et al.; 2019; Hypertension; Italy, UK, Netherland, Poland, France	RCT	1128 healthy participants (503/625)	70.8	1 year	MedDiet vs HabDiet	N/A	N/A	AIX improved with MedDiet ($p = 0.004$), while PWV did not show any significant changes.	N/A	SBP experienced a significant decrease in the MedDiet group. While DBP did not show any significant changes.

Table 1. Study Characteristics (continue…)

Author; Year; Journal; Country	**Study design**	**Sample Size (M/F)**	**Mean age (years)**	**Intervention Duration**	**Type of Diet**	**Results and Conclusions**				
						Lipid Profile	**Inflammatory Markers**	**Atherosclerosis Progression**	**Anthropometry**	**Blood pressure**
Jimenez-Torres et al.; 2021; STROKEAHA; Spain	RCT, single blind	939 coronary heart disease patients (774/165)	59.6	5 years and 7 years	MedDiet vs LFD	N/A	N/A	MedDiet significantly decreased IMT-CC values after the 5th year ($p<0.001$) and 7th ($p<0.001$) and decreased carotid plaque height compared to baseline. There was no change in BMI-CC in the low-fat diet group in years 5 and 7.	N/A	N/A
Landry MJ et al.; 2023; JAMA Network Open; USA	RCT, single blind	44 healthy participants (10/34)	39.6	8 weeks	VD vs omnivorous diet	VD significantly reduced LDL levels compared to an omnivorous diet. ($p = 0.02$)	No significant difference in TMAO concentration was found between the two groups.	N/A	VD significantly reduced body weight compared to an omnivorous diet. ($p = 0.01$)	N/A
Turner-McGrievy GM et al.; 2023; JAMA Network Open; USA	RCT, , single blind	159 overweight/obese participants (33/126)	48.4	12 months	*Vegan soul food diet*vs low-fat omnivorous soul food diet	There was no difference in lipid profile between the two groups.	N/A	N/A	No significant difference in body weight was found between the two groups.	No significant difference in blood pressure was found between the two groups.

Table 1. Study Characteristics (continue…)

Author; Year; Journal; Country	**Study design**	**Sample Size (M/F)**	**Mean age (years)**	**Intervention Duration**	**Type of Diet**	**Results and Conclusions**				
						Lipid Profile	**Inflammatory Markers**	**Atherosclerosis Progression**	**Anthropometry**	**Blood pressure**
Lupoli R et al.; 2024; Biomedicines; Italy	RCT, single blind	25 overweight/ obese participants (12/13)	42	8 weeks	MedDiet vs HabDiet	N/A	N/A	MedDiet was able to improve endothelial function as measured by FMD. There was a significant increase in FMD results in the MedDiet group compared to HabDiet at T0-2h (p 0.004), T8w-fasting (p 0.008) and T8w-2h (p 0.003).	N/A	N/A
Murphy KJ et al.; 2022; Nutrients; Australia	RCT	108 healthy participants	75	18 months	MedDiet vs HabDiet	No significant decrease in lipid profile was found in either the MedDiet or HabDiet groups.	No significant changes in CRP were found at 18 months in either group.	N/A	No significant changes were found in body weight and BMI after 18 months of intervention in both groups.	There were significant differences in SBP (p = 0.001) and DBP (p = 0.008) after 18 months compared to baseline in theHabDiet group, but not in the MedDiet.

Table 1. Study Characteristics (continue…)

Author; Year; Journal; Country	Study design	Sample Size (M/F)	Mean age (years)	Intervention Duration	Type of Diet	Results and Conclusions				
						Lipid Profile	Inflammatory Markers	Atherosclerosis Progression	Anthropometry	Blood pressure
Millan-Orge et al.; 2021; Scientific reports; Spain	RCT	664 coronary heart disease patients	59.3	6 years	MedDiet vs LFD	N/A	N/A	MedDiet and LFD can improve microvascular endothelial function as indicated by increased BF and RHA.	N/A	N/A
After all, DWK et al.; 2024; Am J Clin Nutr; Singapore	RCT, , single blind	89 healthy participants (35/54)	59	8 weeks	PBMD vs ABMD	No significant changes were found in the lipid profile between the two groups.	There was no difference in CRP levels between the two groups.	N/A	No effect of the intervention on body weight and BMI was found. However, there were some significant changes in waist-to-hip ratio values during the PBMD intervention.	N/A
Yuberro EM et al.; 2020; PLOS Medicine; Spain	RCT, single blind	805 coronary heart disease patients (744/61)	60.2	1 year	MedDiet vs LFD	N/A	N/A	There was a significant increase in FMD on MedDiet compared to LFD (p 0.011)	N/A	N/A

Table 1. Study Characteristics (continue…)

Author; Year; Journal; Country	**Study design**	**Sample Size (M/F)**	**Mean age (years)**	**Intervention Duration**	**Type of Diet**	**Results and Conclusions**				
						Lipid Profile	**Inflammatory Markers**	**Atherosclerosis Progression**	**Anthropometry**	**Blood pressure**
Tsaban G et al.; 2020; BMJ; Israel	RCT	294 participants with obesity/dyslipidemia (259/35)	51.1	18 months	HDG, MedDiet, Green-MedDiet	There was a greater reduction in LDL levels on the Green-MedDiet. MedDiet and Green-MedDiet had similar results in increasing HDL levels and decreasing triglyceride levels.	HsCRP concentrations were significantly reduced in the Green-MedDiet group compared to the HDG and MedDiet groups.	N/A	Green-MedDiet and MedDiet showed greater weight loss compared to HDG. Green-MedDiet reduced waist circumference more than the other two groups.	Green-MedDiet showed greater blood pressure reduction compared with MedDiet and HDG.
Zelicha H et al.; 2024; Obesity; Israel	RCT, single blind	290 participants with obesity/dyslipidemia (256/34)	51.1	18 months	Green-MedDiet, MedDiet, and HDG	N/A	Green-MedDiet and MedDiet caused a significant decrease in pro-inflammatory proteins, including IL-1ra, IL-16, IL-18, etc. ($p < 0.05$).	N/A	N/A	N/A

Table 1. Study Characteristics (continue…)

Author; Year; Journal; Country	Study design	Sample Size (M/F)	Mean age (years)	Intervention Duration	Type of Diet	Results and Conclusions				
						Lipid Profile	Inflammatory Markers	Atherosclerosis Progression	Anthropometry	Blood pressure
Urpi-Sarda M et al.; 2021; Biomedicine; Spain	RCT, single blind	285 participants with high risk of cardiovascular disease (96/189)	67	3 years	MedDiet-EVOO vs MedDiet-Nuts vs LFD	There was a decrease in total cholesterol and triglycerides in all three groups; LDL levels decreased in both MedDiet groups; LFD showed significant improvement in HDL levels.	MedDiet-EVOO and MedDiet-Nuts showed significant reductions in inflammatory biomarkers ($p < 0.05$). There was a decrease in IL-1β, IL-6, IL-8, and TNF-α significantly after MedDiet intervention compared to the LFD group ($p < 0.05$).	N/A	The MedDiet-EVOO group experienced significant weight loss (p (0.05).	There was a significant decrease in DBP in all three intervention groups. There was no significant difference in SBP.

RCT: Randomized Controlled Trial, LDL: Low–density Lipoprotein, HDL: High–density Lipoprotein, TMAO: Trimethylamine N-oxide, IGF-1: Insulin-like Growth Factor 1, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, MedDiet: Mediterranean Diet, LFD: Low Fat Diet, RHI: Reactive Hyperaemia Index, AIX: Augmentation Index, VD: Vegetarian/Vegan Diet, MD: Meat Diet, hs-CRP: High sensitivity C-reactive Protein, IMT: Body Mass Index, MedDiet-EVOO: Mediterannean Diet Enriched/Extra Virgin Olive Oil, MedDiet-Nuts: Mediterannean Diet + Mixed Nuts, HabDiet: Habitual Diet, AIX: Augmentation Index, PWV: Pulse Wave Velocity, IMT-CC: Intima-Media Thickness Common Carotid Arteries, FMD: Flow-mediated Dilation, BF: Basal Flow, RHA: Reactive Hyperaemia Area, CRP: C-reactive Protein, PBMD: Plant-based Meat Analog Diet, ABMD: Animal-based Meat Diet, HDG: Healthy Dietary Guidance, Green-MedDiet: Green Mediterranean Diet, IL-1β: Interleukin 1β, IL-6: Interleukin 6, IL-8: Interleukin 8, TNF-α: Tumor Necrosis Factor α, IL-1ra: Interleukin-1 receptor antagonist.

giving antioxidant effects by inhibiting LDL oxidation.[32–34] Hazelnuts consist of high PUFA content, walnuts are rich in MUFA, while peanuts contain higher amounts of protein and fiber compared to other kind of nuts. Fiber consumption induces hypocholesterolaemic effect by the binding with bile acids, thus reducing cholesterol levels in circulation. Furthermore, the fermentation of fiber in the colon produces acetate, propionate, and butyrate which can prevent cholesterol synthesis.[32,33]

Several inflammatory markers of atherosclerosis include C-reactive protein (CRP), interleukin-6 (IL-6), and IL-1 receptor antagonists. While some inflammatory biomarkers specific in atherothrombosis are platelet aggregation markers (P-selectin, platelet factor-4), coagulation markers (fibrinogen, prothrombin factor 1+2), and the decrease of fibrinolysis indicators such as plasminogen activator inhibitor-1 (PAI-1) and d-dimer. Endothelial activation markers such as CRP, E-selectin, soluble intercellular adhesion molecule (ICAM-1), and soluble vascular cell adhesion molecule (VCAM-1), tend to elevate in individuals with higher trans-fat intake, potentially contributing to inflammation and dysfunction of endothelium. This chronic inflammatory condition of arterial wall is mediated by phagocytic leukocytes, including monocytes and macrophages. This pathological process begins with the accumulation of LDL in subendothelial layer of blood vessels which then undergoes initial oxidation.[35] Advanced oxidation results in fully oxidized LDL (ox-LDL), later to be ingested by macrophages through scavenger receptors, transforming it into foam cells, the primary sign of early fatty streak lesions. Adhesion molecules like ICAM-1 mediate the release of endothelial adhesion glycoproteins, which controls leukocyte attachment to endothelial cells. This accumulation of lipids, fibrotic elements, and calcification leads to the formation of atherosclerotic plaques.[35,36]

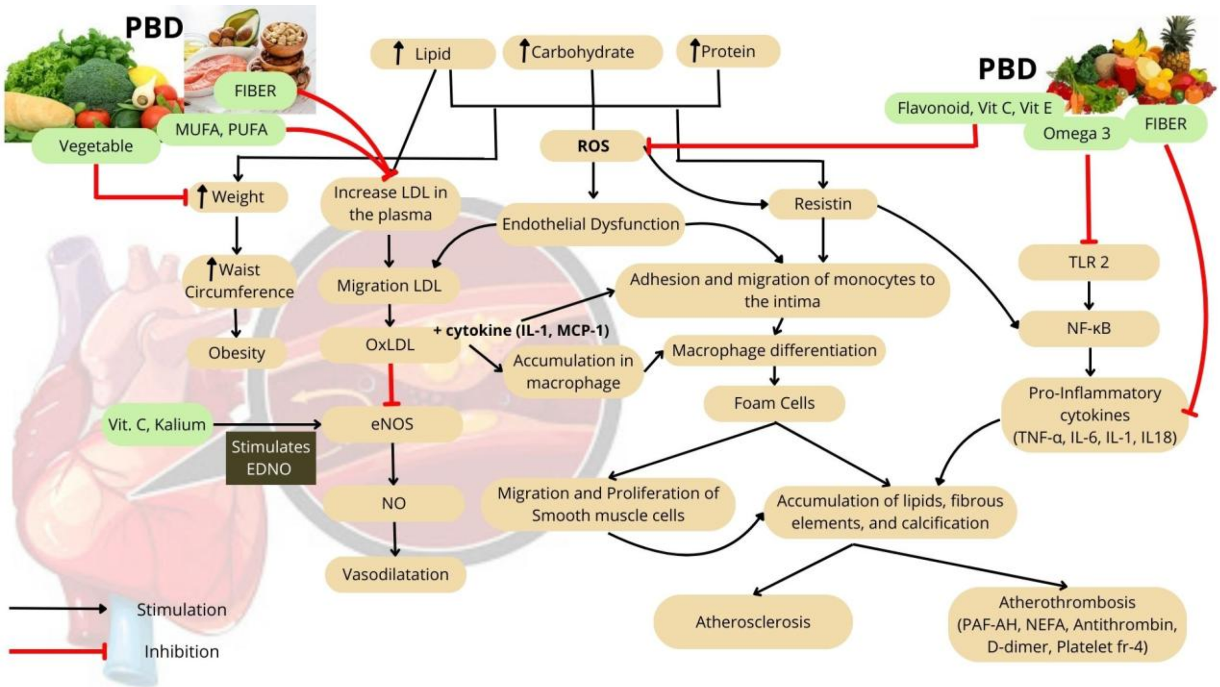
PBD contains high level of polyphenols, which are natural antioxidants produced by plants. According to previous in vitro research, polyphenols have a strong antioxidant potential through their ability to neutralize reactive oxygen species (ROS) via electron donation and hydrogen transfer.[34] This antioxidant property can modify nitric oxide (NO) synthesis, which enables endothelial function protection. Low-fat, low-cholesterol, low-sodium, and low-red meat diets can reduce vascular endothelial cell (VEC) injury. Polyphenols can inhibit LDL oxidation and prevent ox-LDL-induced monocyte adhesion to VECs, restrict monocyte transformation into macrophages, and disrupt foam cell formation. Additionally, avoiding red meat may suppress the formation of trimethylamine-N-oxide (TMAO), a potential contributor in atherogenesis. TMAO can enhance platelet aggregation, decrease NO bioavailability, and increase macrophage infiltration into blood vessels.[32,33,37] A protein named resistin is created in reaction to oxidative stress, inflammation, and metabolic changes, contributing to atherosclerosis progression as proinflammatory mediator in the differentiation of macrophage.[17] Omega-3 content in fish, nuts, and plant seed oils exerts anti-inflammatory effects by linking to G-protein-coupled receptor 120 (GPR120) that inhibits macrophage activation and toll-like receptor 2 (TLR2) expression of pro-inflammatory cytokines.[33]

Out of ten studies that evaluate the relationship between PBD and inflammatory markers, seven showed a significant improvement of inflammatory marker profile (IL-1β, IL-6, IL-8, TNF-α, CRP, TMAO, and resistin) after PBD intervention. Only one study by Djekic et al, which compared vegan and meat-based diets, that found no significant difference in trimethylamine N-oxide (TMAO) levels. These findings may have been influenced by factors beyond dietary patterns, including participants' metabolism and renal function.[14]

Plaque accumulation due to inflammatory processes can lead to vascular dysfunction, potentially resulting in ischemia and tissue necrosis. Ultrasound evaluation in this study includes measurements of arterial stiffness, carotid artery intima-media thickness, and flow-mediated dilation (FMD). Pulse wave velocity (PWV) and augmentation index (AIx) were used to assess arterial stiffness.[38] Only study by Jennings et al that found no changes in PWV, although there was a significant increase in AIx between intervention and control groups. Possible explanation for this may be because Mediterranean diet is known to reduce systolic blood pressure in small blood vessels but not in elastic aorta, thus improvement of AIx was found without significant changes in PWV.[29]

Vitamin C and E, beta-carotene, potassium, omega-3 fatty acids, omega-6 fatty acids, and magnesium were some of antioxidant minerals that can be found in PBD. Vitamin C and potassium stimulate the synthesis of endothelial-derived nitric oxide (EDNO). EDNO acts as a cofactor for endothelial nitric oxide synthase (eNOS), which facilitates the conversion of L-arginine into nitric oxide (NO). NO serves as a primary vasodilator, which prevents the proliferation of vascular smooth muscle by reducing leukocyte and platelet activation.[35,39] High potassium intake contributes to blood pressure reduction and lower risk of cerebrovascular diseases by improving endothelial function and vascular equilibrium. Magnesium can also improve many cardiometabolic parameters, primarily through its role in glucose metabolism and its anti-inflammatory properties.[32,40,41] Omega-3 fatty acids play a significant role in reducing blood triglyceride levels by decreasing the hepatic secretion of triglyceride-rich lipoproteins. In addition to modulating lipid profiles, omega-3 fatty acids, particularly docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), serve as precursors for bioactive lipid mediators involved in anti-inflammatory processes. This activity contributes to a reduction in the production of inflammatory mediators such as prostacyclin (PGI2), thromboxane A2 (TXA2), and other pro-inflammatory compounds that are key components in the pathogenesis of atherosclerosis.[42] Meanwhile, omega-6 fatty acids have been shown to reduce blood pressure and improve insulin sensitivity, thereby exerting a protective effect against cardiovascular risk.[43] Majority of the research findings presented in this review reported significant reduction in blood pressure measurement after the intervention of PBD. However, the rest reported nonsignificant results, likely due to participants' noncompliance with prescribed dietary interventions.[19–22]

Previous review suggests that PBD contribute to short-term weight loss and long-term weight gain prevention,[32] reducing cardiovascular risk in the long run. Gut microbiota may also have an impact on the link between PBD and metabolic factors. The Men's Lifestyle Validation Study (MLVS) found that individuals with higher healthy plant-based diet index scores (hPDI) exhibited distinct gut microbiota profiles, elevated branched-chain amino acid (BCAA) biosynthesis pathways, and reduced animal-derived metabolic pathways.[35] The high fiber content in PBD contributes to an increase in satiety, reducing hunger, and decrease energy intake and body weight.[41] A study by Sarda found that after three years of intervention, individuals in MedDiet-EVOO group had significantly reduced body weight and body mass index (BMI).



MUFA: monounsaturated fatty acids; PUFA: polyunsaturated fatty acids; LDL: low density lipoprotein ; OxLDL: Oxidative LDL; TLR2: toll like receptor 2; IL: interleukin; MCP-1: monocyte chemoattractant protein-1; EDNO: Endothelial derivided nitric oxide synthesis; eNOS: endothelial nitric oxide synthase; NO: nitric oxide; NF-κB: Nuclear Factor Kappa B; PAF-AH: Platelet Activating Factor Acetylhydrolase; NEFA: Nonesterified fatty acids

Figure 2. **The Role Of A Plant-Based Diet In The Pathogenesis Of Atherosclerosis.**

However, this study has several limitations. These includes a relatively small number of articles reviewed, heterogeneity in participants' clinical characteristics, adherence variability to PBD, and socio-demographic status. Therefore, more rigorous RCTs are required to validate these connections. Future research is warranted to further explore the potential of PBD in preventing non-communicable diseases (NCDs), including conditions such as cardiovascular diseases, cancers, chronic respiratory diseases, and diabetes. PBD patterns may be recommended and implemented as a daily nutritional approach for the general population and individuals at risk, to prevent the development of CHD and other atherosclerotic conditions.

These results have significant relevance especially for public health. In primary prevention, PBD has the potential to reduce the risk of atherosclerosis by preventing plaque formation. In individuals with CHD, the cardioprotective effects of PBD, including improvements in inflammatory markers associated with atherothrombosis and the antioxidant properties that support endothelial function, may help slow disease progression and contribute to increased life expectancy. Furthermore, this review reinforces the scientific basis for evidence-based nutritional guidelines, as its findings aligned with the American Heart Association (AHA) heart-healthy diet recommendations.

The strength of this review lies in its comprehensive analysis of the effects of PBD on atherosclerosis-related biomarkers, structural and functional vascular changes caused by atherosclerosis progression, and risk factors that accelerate atherosclerosis development both in at-risk individuals and CHD patients. Additionally, this review assessed both overall and specific benefits of a healthy PBD. Given that CHD is a leading cause of death in the world, this information is anticipated to serve as valuable reference for healthcare professionals in educating general public and as a foundation for future research.

CONCLUSION

This systematic review supports the intervention of PBD in improving atherosclerosis biomarkers for individual at-risk and patient with CHD, primarily by reducing systemic inflammation and improving lipid profiles. These changes include reductions in pro-inflammatory cytokines (e.g., IL-6, CRP) and atherogenic lipids such as LDL cholesterol, alongside increases in protective markers like HDL. However, the result variability is still high due to differences in participants' adherence to dietary interventions, intervention duration, and the type of PBDs applied (e.g., vegan, Mediterranean, vegetarian). Despite the limitation, the overall evidence from this review still confirms the role of PBD in lowering key cardiovascular risk factors, slowing atherosclerosis progression, and potentially reducing morbidity and mortality related to CHD. Further research with more homogenic and larger sample size, especially in arterial stiffness assessment is needed, as it directly reflects vascular changes linked to atherosclerosis progression, to provide more objective evidence on the impact of PBD on the prevention and management of CHD.

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