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Omega 3 versus Omega 6 Polyunsaturated Fatty Acids in Cardio-Metabolic Health

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Abstract

Background: Cardiometabolic diseases like type 2 diabetes, metabolic syndrome, heart failure, and other cardiovascular complications are the leading cause of mortality and morbidity across the globe. These conditions are directly attributed to modifiable behaviors such as sedentary activity, poor diet, excessive consumption of alcohol, or smoking. Efforts aimed towards their prevention and management are, therefore, not only essential in the accomplishment of the healthy populations but also for eliminating the associated cost and health burdens. Dietary change is an important approach to the promotion of cardiometabolic health. Omega 3 (C_{20-22} ω 3) polyunsaturated fatty acids have pleiotropic effects on the functioning of cells, control inflammatory factors, and cellular events in vascular endothelial cells and cardiomyocytes. The hypolipemic, anti-arrhythmic, and anti-inflammatory properties of fatty acids offer cardioprotection. Government agencies and national heart associations recommend increased consumption of omega 3 polyunsaturated fatty acids (PUFA) supplements and fish to prevent cardiometabolic diseases.

Purpose of the Study: The purpose of this study is to investigate the role played by ω-3 and ω-6 polyunsaturated fatty acids in promoting cardiometabolic health.

Methods: The research study searched databases such as MEDLINE®, Embase, PsycINFO, CINAHL® and the Cochrane Library for relevant research studies evaluating the function/benefits of polyunsaturated fatty acids particularly ω-3 and ω-6 polyunsaturated fatty acids in promoting cardiometabolic functions published between 2011 and 2020. A total of 77 research studies were identified and used in the meta-analysis.

Results: Results from the meta-analysis indicated that polyunsaturated fatty acids lower the risk for cardiovascular disease by limiting inflammation of blood vessels, reducing thrombosis, increasing levels of high-density lipoproteins, reducing levels of low-density lipoproteins, and reducing risk factors associated with hypertension.

Conclusion: Given the benefits of polyunsaturated fatty acids lower the risk for cardiovascular diseases indicted in the meta-analysis. Therefore, human diets must contain the required amounts of PUFA due to the associated benefits.

Keywords

Omega-3, Omega-6, Polyunsaturated fatty acids, Cardiometabolic health

Background

Cardiometabolic Syndrome is a combination of metabolic dysfunctions characterized by impaired glucose tolerance, insulin resistance, hypertension, dyslipidemia, and central adiposity [1]. Cardiometabolic health encompasses metabolic and cardiovascular diseases [2]. Examples of cardiovascular diseases include heart failure, heart attack, and cardiomyopathy, among others, while metabolic complications include type 2 diabetes and metabolic syndrome [3]. According to [4], cardiometabolic diseases pose significant health and economic burden to the world with high prevalence rates expected. Other factors that predispose individuals to cardiometabolic diseases include a poor diet, sedentary lifestyle, short sleep duration, and prolonged sitting that are significant elements of the modern lifestyles [5]. Cardiometabolic diseases share risk factors, as evident in the impact of obesity/overweight and elevated blood pressure that can be modified through lifestyle choices and proper diet [6]. PUFAs are fatty acids containing more than one double bond in their chain with examples including omega-3 (ω-3), omega-6 (ω-6), and omega-9 (ω-9) fats [7]. PUFAs can be easily obtained from various food products to enhance cardiometabolic health. This article reports the impact of omega-3 and omega-6 PUFAs in the promotion of cardiometabolic health.

Methods

Database Searches:

The research study employed systematic meta-analysis to analyze different research studies. Concerning this, a systematic computerized literature search of EMBASE, PubMed, PsycINFO, MEDLINE as well as CINAHL databases was performed for different research studies published in English up to February 2020. Generally, the search was conducted by combining a number of keywords as well as medical subheadings; furthermore, no limitations with regard to the search strategy were inserted. Some of the keywords used in the searches included**:** Omega-3, Omega-6, Polyunsaturated fatty acids, cardiometabolic health. On the other hand, some of the medical subheadings included cardiometabolic health benefits of Omega-3 and Omega-6, respectively. References from all the relevant literature were carefully hand searched from these databases and also used to identify additional relevant research studies. Following the initial search, a total of 151 relevant articles were located.

Article Screening Methods:

Literature search yields hundreds to thousands of candidate documents where most of them get excluded after screening because they are not relevant to the topic under study. Screening candidate articles in a systematic review for inclusion takes much time when conducted manually [8]. Automated tools dedicated to screening candidate studies were employed to reduce human effort and to arrive at the main objective within a shorter period. The methods used are based on supervised machine learning techniques. Based on trained models, they were able to identify relevant keywords in the abstract of candidate articles. Keywords used here included omega 3, omega 6, cardiometabolic diseases, polyunsaturated fatty acids, and PUFA. Articles screened were elected from those which were published between 2010 and 2020 to help obtain the latest and most relevant information. The screening exercise yielded to 114 articles that were relevant to this topic and had the latest information about the contribution of omega 3 and 6 to cardiometabolic diseases. The screening method excluded those studies which did not meet a predefined set of characteristics. The results obtained were compared to the actual reviews inclusion list. The screening threshold rule used identified studies that mentioned Polyunsaturated fatty acids (PUFAs) and Cardiometabolic health in the study abstract. This rule excluded 91.6% of studies retrieved.

Inclusion and Exclusion Criteria:

An exclusion/inclusion criterion used ensured that the selection of studies was unbiased and that the article selected focused on the main research question. An exclusion/ inclusion criterion was employed to first screen abstracts and tittles related to cardiometabolic diseases, omega 3, and omega 6 polyunsaturated fatty acids. The next full text was retrieved from these articles and screened to determine whether the content fits the eligibility criteria of this task. Covidence, which is an online systemic review management tool, was

employed to offer independent abstract/ title screening, data extraction, full-text screening, and risk of bias assessment. To selected quality sources, the criteria, thus, for the inclusion of research articles were as follows: the research study had to evaluate the function/benefits of polyunsaturated fatty acids, particularly ω-3 and ω-6 polyunsaturated fatty acids in promoting cardiometabolic functions. The second criteria are that the research had to be published between 2010 and 2020 to ensure relevancy. The third criterion that the research studies had to focus on human beings as opposed to animal studies. However, there were no limitations on the type of research paper included in the research study. After exclusion, a total of 20 high-quality research studies were acquired to be used in the research study, while 56 low-quality research studies were excluded.

Results

Crowe-White et al. (2018) reported that different fatty acids have varying effects on cardiometabolic health [9]. For instance, the ratios of ω-3 to ω-6 is not only essential in the production of eicosanoid metabolites that influence the inflammatory and homeostatic responses but also critical in the pathogenesis of diseases like diabetes [10,11]. The imbalances between the intake of ω-3 and ω-6 may lead to the imbalances in gene-nutrient interactions and endogenous mediators that may lead to biological consequences that influence the disease risk [12,13]. Other studies by [14,15] emphasized the need for replacing saturated fats with unsaturated fats as part of dietary controls towards the management of cardiovascular diseases. Similarly, [9] asserted that the intake of ω-3 and ω-6 PUFAs is beneficial for lowering the risks for cardiometabolic conditions while [16] emphasized the important role played by the two fatty acids in the regulation of the platelet function and thrombosis.

The effect of using omega-3 and omega-6 has been illustrated in various studies. Mozaffarian (2009) examined the combined effect of various omega-3 fats such as EPA and DHA on multiple cardiovascular outcomes has also been revealed [15]. The results indicate the combined dose of EPA and DHA has an anti-arrhythmic effect for weeks, triglycerides lowering for months to a year, heart rate lowering effects for months, and antithrombotic activity for weeks as revealed in (**Fig-1**). Similarly, [17] reported that the average dose of 500mg of either EPA or DHA significantly reduce adverse cardiovascular outcomes, as revealed in (**Fig-2**).

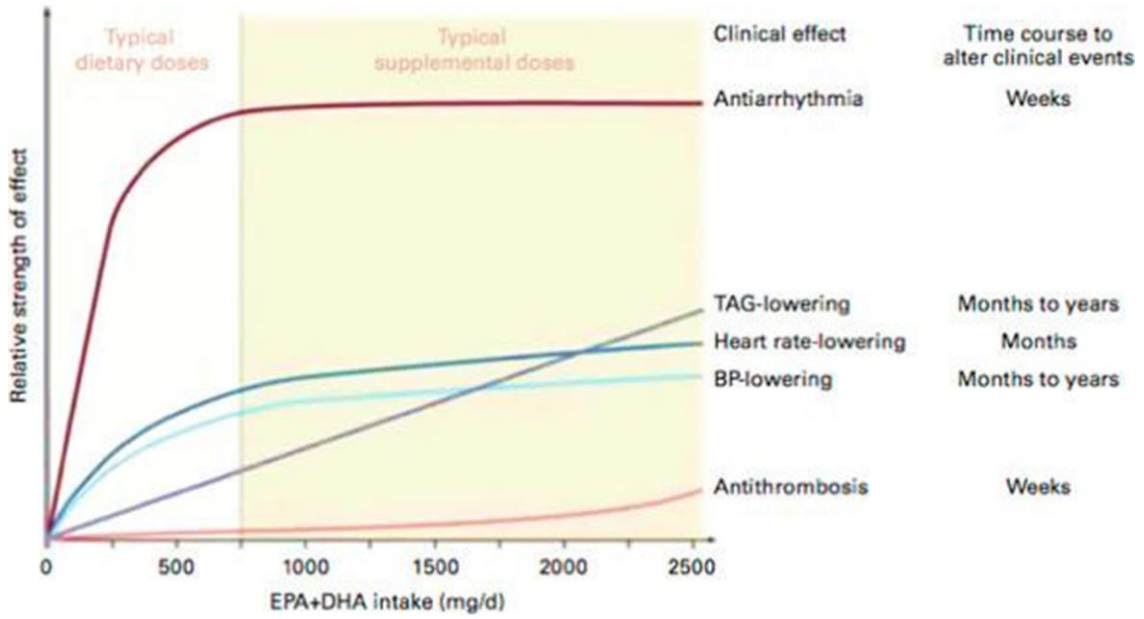

Fig-1:

EPA and DHA relative strength in managing multiple cardiovascular outcomes [15]. Increased consumption of PUFA has the highest effect in reducing anti-arrhythmic followed by reducing triglycerides, lowering the blood pressure and antithrombosis.

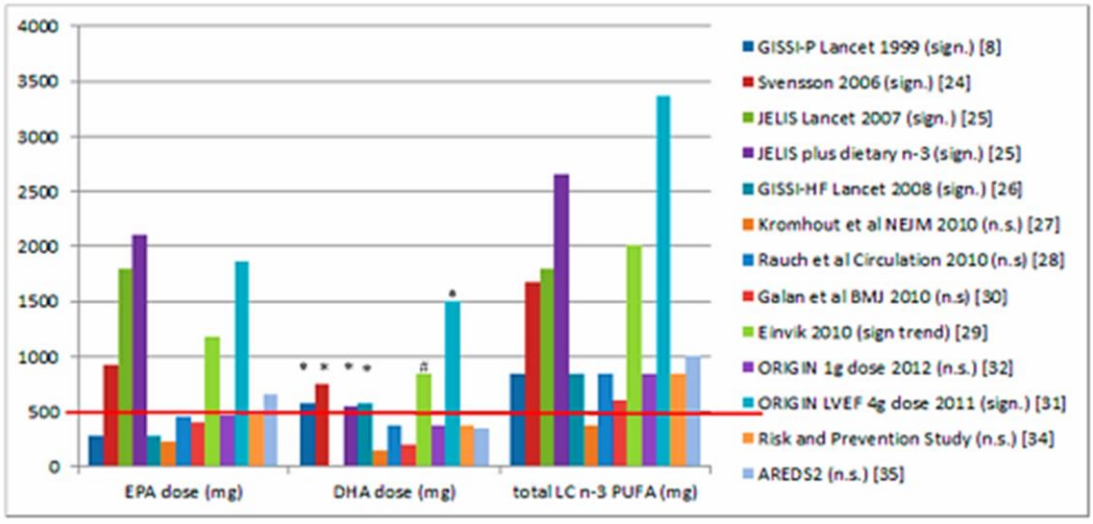

Fig-2:

EPA and DHA that reduce cardiovascular outcomes. The redline represent the average dose of 500mg of either EPA or DHA which is linked with positive outcomes. Adapted from [17].

Impact of ω-3 and ω-6 PUFAs in Inflammation and Cardiometabolic Health:

Inflammation is vital for people's survival by providing protection against infection and injury [18]. However, excessive inflammation is a driver to some diseases like heart diseases, metabolic syndrome, arthritis, cancers, and Alzheimer's [19]. The establishment of the link between inflammation and cardiometabolic diseases, therefore, requires the development of the pharmacological and therapeutic strategies that are intended at the reduction of the inflammatory processes [20]. Diet contributes to inflammation due to the impact of the various proinflammatory substances like the cytokines that influence the mechanisms contributing to the cardiometabolic diseases [21]. For instance, the atherogenesis mechanism that influences the development of acute cardiovascular events arises from inflammatory processes [22]. Omega-3 and omega-6 PUFAs are critical elements of diet intake that significantly influence the occurrence of inflammation in the body and hence influence the status of cardiometabolic health of the individuals [23,24].

Despite the similarities in the benefits of ω-3 and ω-6 PUFAs in cardiometabolic health, the two fatty acids are associated with certain differences [25]. For instance, while ω-3 fatty acids are known for their anti-inflammatory properties, a high intake of ω-6 PUFAs is associated with inflammation [26]. The intake of ω-3 fatty acids also reduces the production of molecules such as eicosanoids and cytokines that are linked to inflammation [27]. Esser et al. (2015) report that chronic inflammation is linked to cardiometabolic diseases and hence implying that increased intake of ω-6 PUFAs may lead contribute to a high risk of conditions like obesity, cardiovascular disease, metabolic syndrome, and type 2 diabetes [28]. However, the work of [29] dismisses the theory that ω-6 PUFAs do not contribute to the inflammation. On the same note, [30] asserts that there is conflicting evidence regarding whether ω-6 PUFAs are proinflammatory or inflammatory. The work of [25] further states that the consumption of more ω-3 fatty acids is associated with a decreased risk of metabolic syndrome as compared to the consumption of ω-6. High consumption of seed oils contains levels of linoleic acid, which have been indicated to reduce oxidative stress, inflammation, and endothelial dysfunction [31].

Dietary levels of linoleic acid have been implicated in increasing levels of cyclooxygenase 2, resulting in the production of proinflammatory cytokines from arachidonic acid [26]. This explains an increase in linoleic acid lowers levels of arachidonic acid by breaking down proinflammatory cytokines (**Fig-3**). An additional arachidonic independent pathway promotes

or increases the production of oxidized linoleic acid metabolites as well as proinflammatory eicosanoids, which serve to activate NF-kB while at the same time increasing proinflammatory cytokines as well as chemokines [26,32]. In addition, the provision of linoleic acid among individuals at risk of being diagnosed with cardiovascular diseases reduced total cholesterol, triglycerides, body mass index, and systolic blood pressure after a 12 month follow up period, as seen in (**Table-1**).

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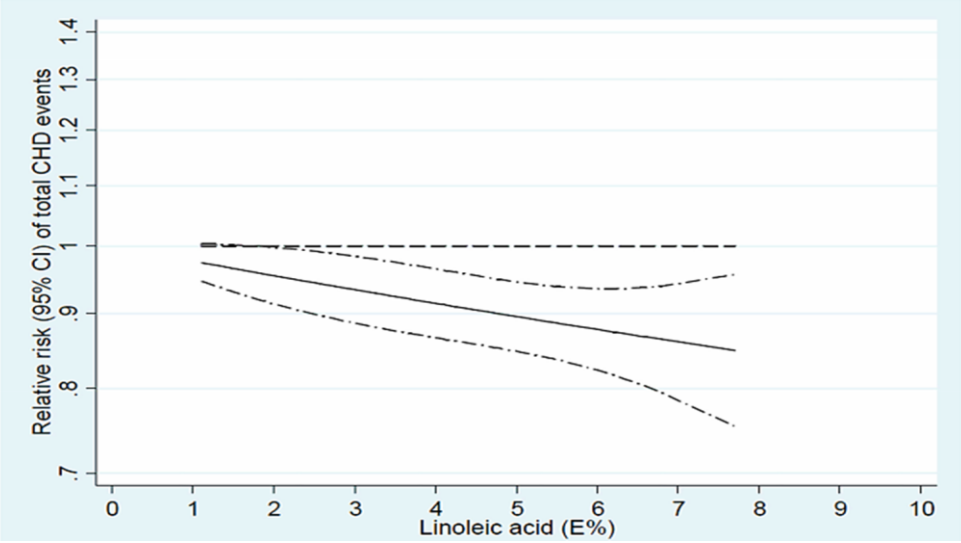

Fig-3:

The relative risk of coronary heart disease on the addition of linoleic acid. Increased consumption of linoleic acid reduces coronary heart disease outcomes [33].

Table-1: Clinical data on changes in cardiovascular outcomes after the provision of linoleic acid following a 12 month follow up. A reduction in the levels of total cholesterol and triglycerides is observed above [34]

	Baseline		12 months follow up		Statistical Significance
	Control	Intervention	Control	Intervention	p-value
Total cholesterol	282	281.3	266.5	243.9	<0.0001
Triglycerides	185.9	189	151.8	136.5	0.06
Body mass index	25.4	25.1	24.5	24.3	0.26
Systolic blood pressure	136.9	136.6	136.5	136.4	0.49
Diastolic blood pressure	88.5	88.5	87.9	87.5	0.38

A key mechanism that results in the down-regulation of the synthesis of proinflammatory cytokines such as interleukin 6, tumor necrosis factor-alpha and monocyte chemoattractant protein-1 occurs in the adipose tissue [34,35]. DHA and EPA bind to G-protein coupled receptors present in the adipocytes and macrophages, resulting in the activation as well as the internalization of β-arrestin-2, and the formation of a complex GPR120/β-arrestine-2 [27]. The complex dissociates to transforming growth factor-beta (TGF-β) activated kinase 1 binding protein 1 (TAB1), which has been implicated in inhibiting and downregulating the activity of nuclear factor kappa B (NF-κB) [36,37]. Incorporating DHA into the lipid membrane also disrupts the activity of toll-like receptor 4 and inhibits several essential pathways related to fatty acid synthesis [27,34,38]. In addition, the presence of DHA and EPA downregulates the activity of nicotinamide adenine dinucleotide phosphate oxidase, which is key to producing reactive oxygen species required in the signaling of TLR-4 [38]. The mechanism linking PUFAs to inflammation is revealed below in (**Fig-4**).

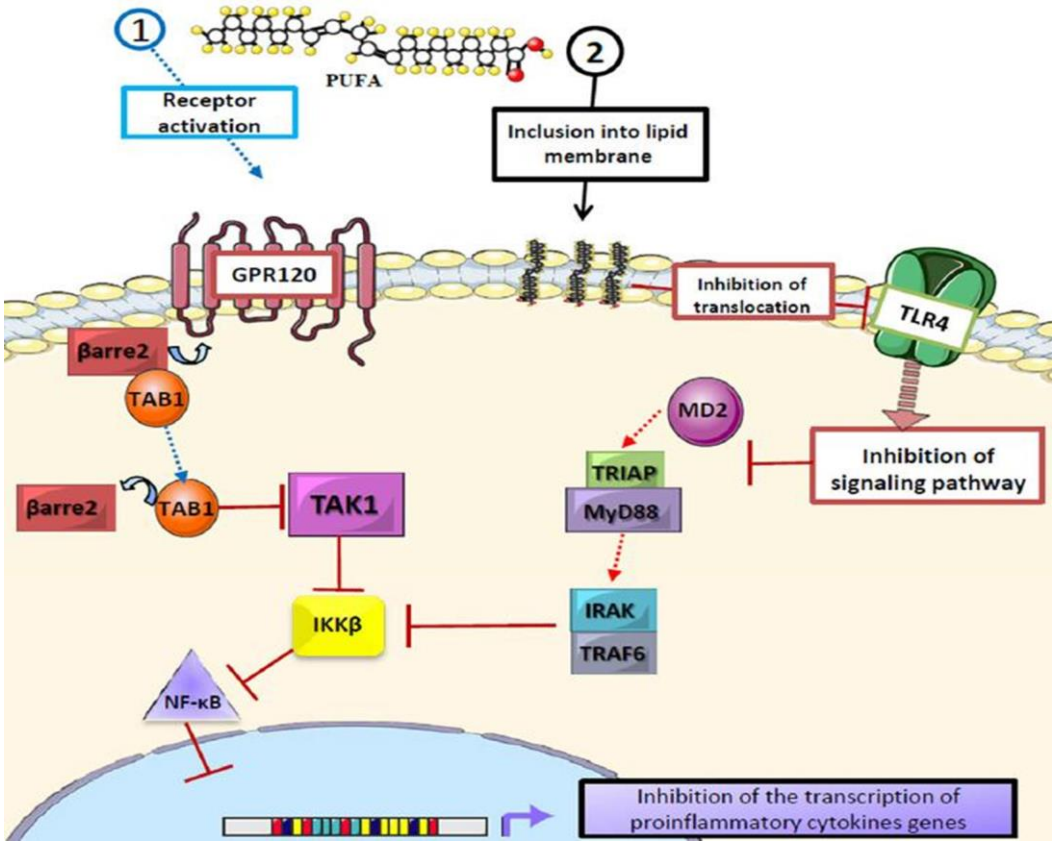

Fig-4:

Roles of PUFA in inhibiting the activities of proinflammatory cytokines. The first step shows the binding of DHA and EPA, resulting in the activation and binding of Beta-arrestin-2, which breaks down to produce TABI, which inhibits TAKI and disrupting the remaining pathways [39].

Impact of ω-3 and ω-6 PUFAs in Hypertension:

Recent studies reveal that maintaining low blood pressure even among individuals not diagnosed with hypertension is essential in reducing the incidences of cardiovascular diseases [39]. PUFAs regulate blood pressure through a number of different mechanisms, with the most common one is promoting the release of renin from the kidney [40]. Diets rich in omega-3 fatty acids have also been shown to suppress the activity of ACE (angiotensin converting enzyme) while at the same time suppressing the formation of angiotensin II which significantly improves the production of endothelial nitric oxide, a potent vasodilator while at the same time suppressing the action of Transforming Growth Factor-Beta [41,42]. The process by which PUFAs reduce the incidence of hypertension is revealed below in (**Fig-5**).

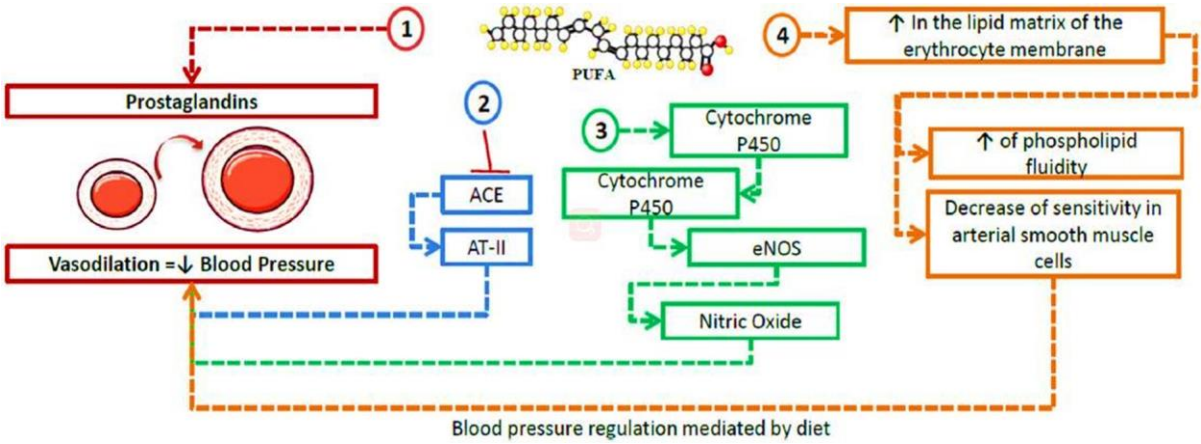

Fig-5:

The role of polyunsaturated fatty acids and their role in managing hypertension. PUFAs. Step 1 shows how arachidonic acid increases vasodilation. The second pathway shows inhibition of ACE on the blood pressure level. The third pathway shows the action of P450 isoforms in nitric oxide production [39].

A meta-analysis carried out by [43] also assessed the efficacy of omega-3 supplementation on pre-eclampsia or hypertension. The meta-analysis revealed which compiled 14 different results indicated that the use of omega-3 fats had a protective effect on pre-eclampsia as indicated by the meta-analysis summary below (**Fig-6**).

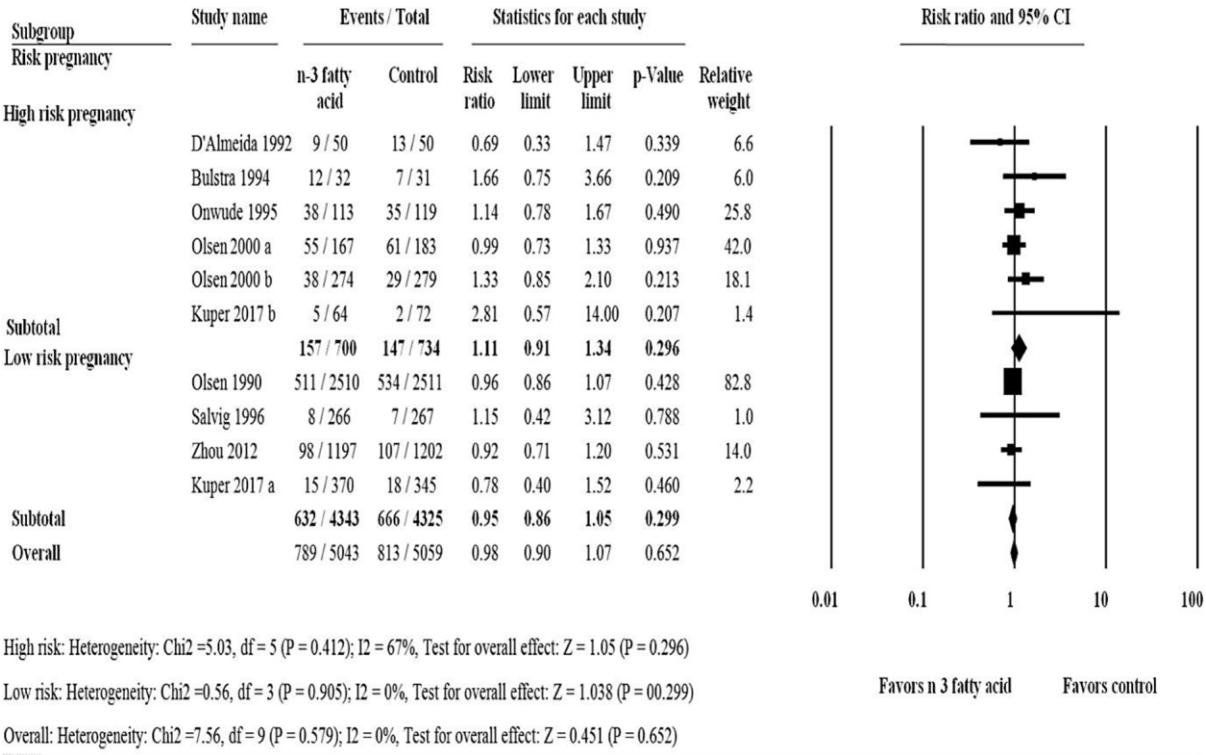

Fig-6:

Meta-analysis results showing the effectiveness of omega-3 supplementation in reducing hypertension.

PUFAs have been shown to induce the formation of nitric oxide, which prevents vasoconstriction [44]. A 6:1 ratio mixture of EPA: DHA was provided to Wister rats. Examined whether chronic intake of induces the function of angiotensin II in rats [45]. The results revealed that the consumption of chronic EPA: DHA ratios prevented Ang-II induced hypertension as well as endothelial dysfunction by limiting the activity of COX-derived oxidative and NADPH oxidase stress. The results have been indicated in (**Fig-7**).

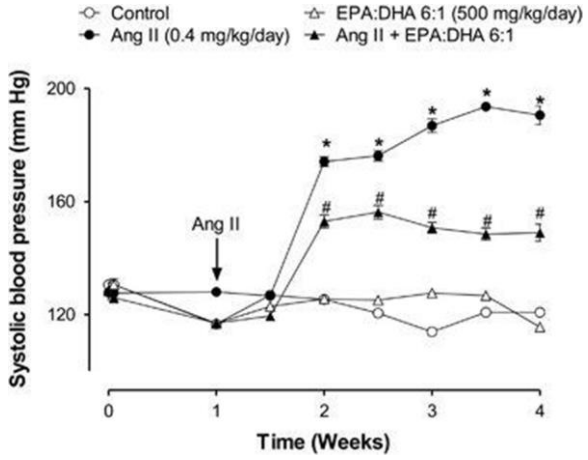

Fig-7:

Chronic intake of PUFAs prevents Angiotensin-II hypertension in rats in the first week when fed orally before the level rises when rats are fed using a somatic pump. The results adapted from [45].

EPA and DHA reduce hypertension by altering various hemodynamic. For instance, the use of oof EPA and DHA has various effects on blood pressure, heart rates, cardiac diastolic filling, and arterial compliance, as summarised in the information provided in (**Table-2**).

Table-2: Effect of EPA and DHA on blood pressure variables [46]

	EPA	DHA
Cardiac hemodynamics	Has minimal effects on blood pressure	Reduces blood pressure level
	Reduces heart rate	Reduces heart rate
	Promotes cardiac diastolic filling	Promotes cardiac diastolic filling
	Promotes arterial compliance	Promotes arterial compliance

Impact of ω-3 and ω-6 PUFAs in Thrombogenesis:

Polyunsaturated fatty acids have been shown to exhibit antithrombotic properties [47]. Available studies indicate that the Eskimo diet that is rich in intake of seafood contains high levels polyunsaturated fatty acids which have been directly linked with low incidences of cardiovascular diseases as well as a decrease in thrombogenesis [48,49]. Most of the above effects have been described in populations found in different areas although the inverse relationship between intake of omega-3 polyunsaturated fatty acids has been associated with platelet aggregation, fibrinolysis, and coagulation has not been completely elucidated [50]. Nonetheless, in-vitro and in vivo studies reveal that the use of polyunsaturated fatty acids supplementation reduces the synthesis of thromboxane 2, platelet adhesion and activation and decreases the concentration and activity of plasminogen activator inhibitor-1 [16,51]. The specific mechanism in which omega-3 polyunsaturated fatty acids decrease levels of thrombogenesis has been studied, especially in platelets.

High levels of common polyunsaturated fatty acids, such as EPA and DHA, favor the replacement of arachidonic acid within the phospholipids of the cell membrane [52]. This decreases the binding of arachidonic acid on cyclooxygenase 1, reducing the synthesis of thromboxane A2, which is considered as an element that increases platelet aggregation and vasoconstriction [52,53]. The approach also produces Thromboxane A3, which exerts a low biological effect compared to thromboxane A2. Another suggested mechanism in which omega-3 polyunsaturated fatty acids reduces thrombogenesis involves the synthesis of protectin DX which is considered a product of dihydroxylation of DHA [54,55]. The product inhibits the activity of cyclooxygenase 1 and cyclooxygenase 2 in neutrophils and platelets, reducing platelet aggregation and activation, as indicated in (**Fig-8**).

DHA and EPA were reported to have minimal effects on thrombosis or coagulation. Furthermore, the use of DHA and EPA are indicated to reduce inflammation and oxidative stress, which have been linked with thrombogenesis. The results are indicated in (**Table-3**).

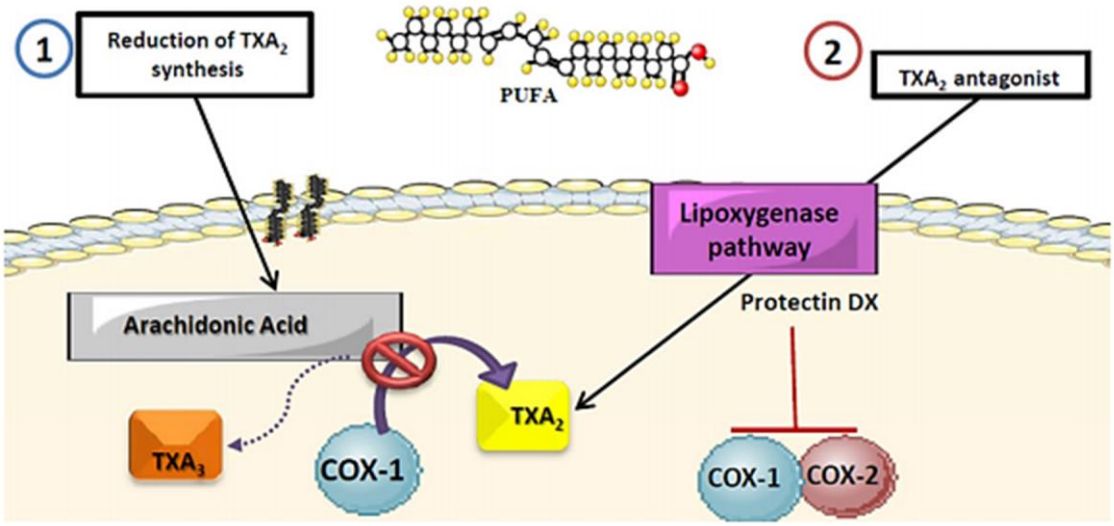

Fig-8:

Role of polyunsaturated fatty acids in thrombogenesis. The first mechanism involves reducing the synthesis of thromboxane A2 and the effect of protectin DX [39].

Table-3: EPA and DHA effect on thrombogenesis related factors [46]

	EPA	DHA
Thrombosis and coagulation	↓ Collagen-stimulated platelet aggregation	↓ Collagen-stimulated platelet aggregation
	Otherwise minimal effects on thrombosis or coagulation	Otherwise minimal effects on thrombosis or coagulation
Endothelial function	Reduces inflammation	Reduces inflammation
	Reduces oxidative stress	Reduces oxidative stress

Human beings associated thromboembolism with endothelial function [56]. Previous studies have already reported on the improved effect of EPA and DHA on the endothelial function of arteries, but the impact on veins is largely unclear [57,58]. [60] report that administration of EPA: DHA in a ration of 6:1 for a week resulted in the release of acetylcholine, which causes relaxation of veins at low concentrations. Also EPA: DHA ratios of 1:1 increased acetylcholine levels resulting in the relaxation of femoral vein. Corn oil did not show any difference (**Fig-9**).

Impact of ω-3 and ω-6 on Lipid Profiles:

Maintaining and monitoring healthy levels of lipids circulating within the bloodstream remains one of the essential methods used to diagnose different cardiovascular diseases [47]. A lipid panel or profile is considered as a group of individual tests that evaluate an individual risk of developing different cardiovascular treatments [60]. Normally, lipid profiles consist of various types of molecules, including total cholesterol, low-density lipoprotein, high-density lipoprotein, and triglycerides [61]. HDL is regarded as the good cholesterol and removes excess cholesterol from arteries and also carries low-density lipoproteins cholesterol back to the liver for decomposition and removal from the body [62,63]. The application of diets rich in either omega-6 or omega 3 fats significantly improves cardiovascular health by directly improving the activity of HDL and lowering levels of LDLs. [64] observed that a diet rich in omega-3 supplementation greatly improved lipid metabolism, reduced triglycerides levels, and increased activity of HDLs as well as anti-platelet activity and anti-inflammatory effects. Similarly, a systematic review and meta-analysis by [1] observed that consumption of polyunsaturated fatty acids was associated with a

decrease in low-density lipoprotein and an increase in high-density lipoprotein which is associated with reduced incidences of coronary heart diseases.

Although there is less recent randomized clinical trials evidence examining the effects of dietary fats on various outcomes, a large body examining the impact of dietary fat on lipid profiles has been reported. A higher level of atherogenic cholesterol or cholesterol carried in non-HDL vesicles, and LDL has been implicated in atherosclerosis [65]. Corn olive oil has been shown to reduce LDL and the total cholesterol level [66]. However, the study by [8] reported no significant effects while comparing the effects on blood lipid after consumption PUFAs, although the study was dominated by findings of one paper. A systematic review by [67] also reported that the use of canola oil reduces low-density lipoprotein but had no effect on high-density lipoproteins. Guidelines in managing the condition are associated with reducing the concentrations of LDL cholesterol. The replacement of saturated fatty acids (SFA) with PUFAs lowers cholesterol LDL and changes the triglycerides: HDL cholesterol level as shown in (**Table-4**).

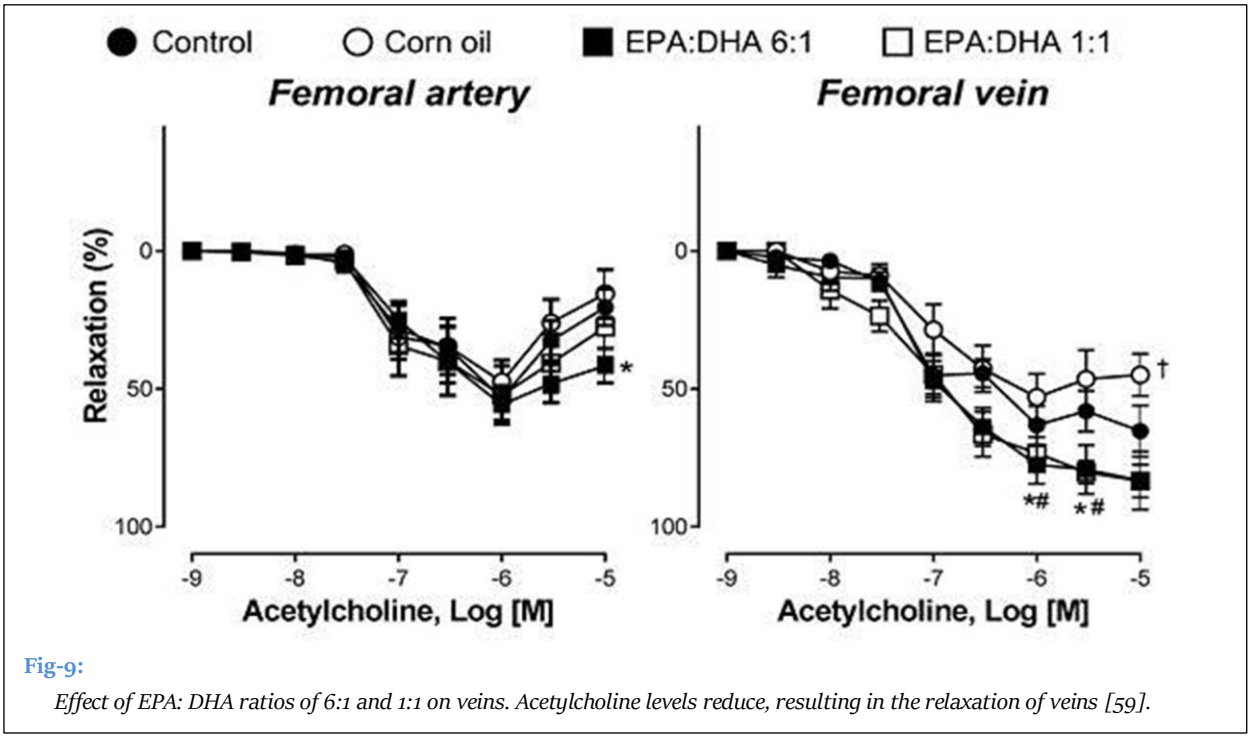

Fig-9:

Effect of EPA: DHA ratios of 6:1 and 1:1 on veins. Acetylcholine levels reduce, resulting in the relaxation of veins [59].

Table-4: Changes in total cholesterol (Total-C), LDL Cholesterol, HDL cholesterol, Total-C/HDL cholesterol and TGs when diets are changed from SFA to carbohydrates(CHO), SFAs to Monounsaturated fatty acid (MUFA) and SFA to PUFAs [68]

Change (mmol/L) per 1% energy replaced			
Lipoprotein lipid	**SFAs → CHO**	**SFAs → MUFAs**	**SFAs → PUFAs**
Total-C	−0.041 (−0.047, −0.035)	−0.046 (−0.051, −0.040)	−0.064 (−0.070, −0.058)
LDL cholesterol	−0.033 (−0.039, −0.027)	−0.042 (−0.047, −0.037)	−0.055 (−0.061, −0.050)
HDL cholesterol	−0.010 (−0.012, −0.008)	−0.002 (−0.004, 0.000)	−0.005 (−0.006, −0.003)
Total-C/HDL cholesterol	0.001 (−0.006, 0.007)	−0.027 (−0.033, −0.022)	−0.034 (−0.040, −0.028)
TGs	0.011 (0.007, 0.014)	−0.004 (−0.007, −0.001)	−0.010 (−0.014, −0.007)

ApoA-I is regarded as the main protein component present in HDL particles, which promotes the maturation of HDL by allowing cholesterol efflux from various cells [69]. It also stimulates cholesterol esterification through the activity of the enzyme lecithin cholesterol acyltransferase (LCAT) [70]. Plasma levels of LCAT increase with the consumption of highly enriched omega-3 oil [17]. Consumption of omega-3 increases the hepatic and plasma expression of ApoA-I and is linked with the anti-oxidative activity of HDLs. ApoA-I stabilises the activity of paraoxonase-1 (PON1) which is linked to HDL [71]. PON1 reduces the oxidative stress associated with macrophages, reduces the production of proinflammatory cytokines [72], and increases cholesterol efflux capacity of macrophages [73], as shown in (**Fig-10**).

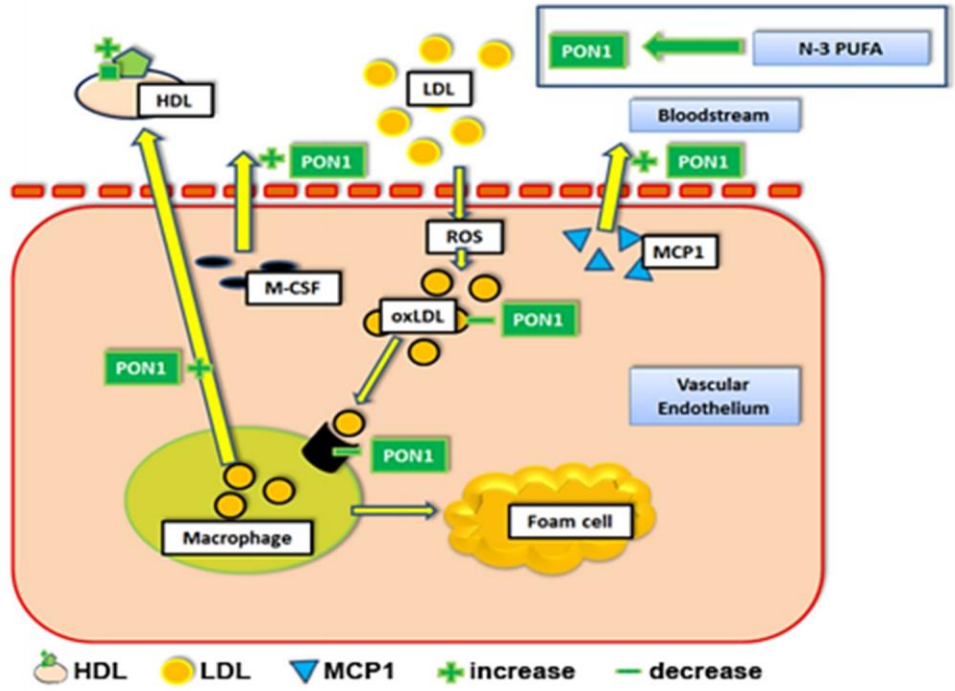

Fig-10:

The effects of omega-3 PUFAs on cholesterol efflux and paraoxonase 1 [74].

The study by [75] reported that lipoprotein apheresis could be used in managing atherosclerosis. Lipoprotein apheresis decreases levels of essential omega 3 and omega 3 PUFAs in blood plasma, but the use of heparin-induced extracorporeal low-density lipoprotein precipitation (HELP) is associated with proinflammatory activity of omega-3 and -6 PUFAs. HELP-treated patients showed cardioprotective effects and limited inflammatory reaction HDL levels increasing and a reduction being observed in HDL and no significant differences being observed in LDL, cholesterol, and triglycerides, as shown in (**Fig-11**). The result recommending omega-3 supplementation in lipid apheresis could have additional benefits.

The blow (**Table-5**) summaries the effect of PUFAs on cardiometabolic health.

Further analysis reveals that the use of EPA and DHA is linked to a reduction in cardiovascular outcomes, as indicated by the relative risks across various studies indicated below (**Table-6**). Individuals who did not take EPA and DHA had higher relative risks of developing coronary heart diseases as compared to those using PUFA [76]. High levels of triglycerides and lipoproteins were also observed among those who did not take PUFA.

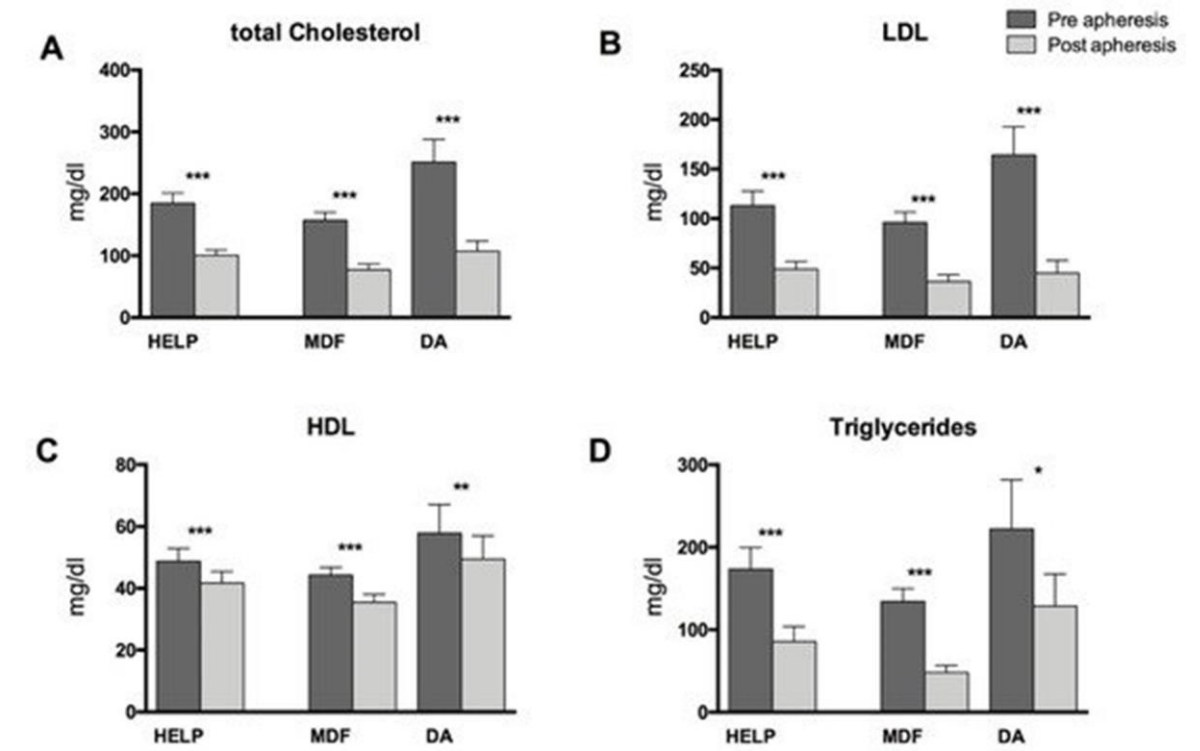

Fig-11:

HELP-treated patients showing differences in lipid profiles [75].

Table-5: The action of PUFA on cardiometabolic health summary [72]

	Omega 3	Omega 6
Cholesterol	EPA and DHA reduces levels of Low-density lipoproteins (LDL) and increases levels of High-Density Lipoproteins (HDL)	Less scientific data on the effect of omega 6 on HDL and LDL levels
Thrombogenesis	Formation of protecin DX which limits the activity of cyclooxygenase 1 and 2	Inhibiting the synthesis of thromboxane A2, which affects the production of arachidonic acid, decreasing the activity of cyclooxygenase 1.
Inflammation	Activation and binding of Beta-arrestin-2, which breaks down to produce TABI, which inhibits TAKI and disrupting the remaining pathways. The presence of DHA and EPA interferes with the translocation of TLR-4, which serves to inhibit the production of cytokines.	Dietary linoleic acid increase s activity of cyclooxygenase 2 which increases the conversion of arachidonic acid to proinflammatory eicosanoid in the process reducing the concentration of arachidonic acid
Blood pressure and hypertension	Conversion of prostaglandins to arachidonic acid and subsequent release of vasodilators like nitric oxide.	Inhibition of ACE and the role of cytochrome p450 in activating nitric oxide

Table-6: A meta-analysis table – table constructed to highlight the main contents of this literature review based on thorough analysis of all the primary research, studies and data involved

Author	Title	Relevance to the topic
[7]	Omega-3, omega-6, and total dietary polyunsaturated fat for prevention and treatment of type 2 diabetes mellitus: Systematic review and meta-analysis of randomized controlled trials.	[7] established elevated LDL-cholesterol as atherosclerosis and CVD risk factor. The research that they conducted demonstrated that increased ω-3 and ω-6 intake had hypocholesterolaemia effects. However, the information provided in their study concerning the specific effects of ω-6 PUFA on blood lipid profiles is limited.
[1]	Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease	Most of the RCT data used by [1] in his study to determine the effects of PUFAs on cardiometabolic diseases was quite old. From his findings, replacement of 5% SFAs by PUFAs significantly reduced CAD risks.
[6]	Overweight, obesity, and risk of cardiometabolic multimorbidity	[6] in their work, conducted a Cochrane meta-analysis where they examined SFA intake reduction and replacing it with PUFA or MUFA. Their research concluded that replacement of SFAs with ω-3 and ω-6 PUFAs resulted in a 17% reduction in cardiometabolic events. They reported that, replacing some saturated fats with PUFAs having plants origin resulted yielded lower cardiometabolic disease risk. Subgroup analysis conducted showed lower risks in PUFA compared to SFA groups.
[11]	Biochemical mechanism of the ratio of omega 6 to 3 fatty acids on blood lipid reduction	[11] literature is relevant to this study, where they conducted a crossectional analysis of Spanish men considered obese. The men underwent laparoscopic gastric bypass surgery. Analysis of the abdominal adipose tissue and venous blood serum was conducted to calculate FA composition. A positive correlation of ω-6 PUFAs with HDL-C and an inverse correlation with triglycerides (TG) was found.
[13]	The ratio of dietary ω-3 and ω-6 fatty acids independent determinants of muscle mass in hemodialysis patients with diabetes.	[13] conducted observational studies among the East Asian and Asian Indian population, which is relevant to this study. They found out through research that, omega 6 PUFAs to be inversely associated with TG across the population studied. A cross-sectional analysis conducted on male cohort found serum LA to be positively associated with HDL-C particle size and inversely associated with LDL-C and VLDL particle sizes.
[15]	A systematic review of the effect of dietary saturated and polyunsaturated fat on heart disease	[15] carried out a meta-analysis of 80 controlled interventional trials where they concluded that n-6 PUFA has beneficial effects on blood lipid levels. The total PUFAs can be considered to be equal to omega 6 PUFA with a number of 18 carbons.
[22]	Inflammatory markers and extent and progression of early atherosclerosis: Meta-analysis of individual-participant-data from 20 prospective studies of the PROG-IMT collaboration.	Their research associated a reduction in blood pressure with a reduction in CVD risks. They concluded in their research that dietary LA is inversely associated with blood pressure (BP)
[29]	The associations of serum n-6 polyunsaturated fatty acids with serum C-reactive protein in men: The Kuopio Ischaemic Heart Disease Risk Factor Study	Cardiometabolic conditions are directly attributed to modifiable behaviors such as sedentary activity and poor diet. Omega 3 (C_{20-22} ω 3) polyunsaturated fatty acids have pleiotropic effects on the functioning of cells, control inflammatory factors and cellular events in vascular endothelial cells and cardiomyocytes. The hypolipemic, anti-arrhythmic, and anti-inflammatory properties of fatty acids offer cardioprotection.

Conclusion

Cardiometabolic diseases are significant health and economic burden globally since they contribute to preventable mortality and morbidity in individuals of all ages, races, and genders. One of the most effective approaches towards the prevention and management of cardiometabolic diseases include lifestyle and dietary changes. Based on the meta-analysis, ω-3 and ω-6 PUFAs are essential fatty acids in the body functioning, and since they are not synthesized in the human body, they are mostly consumed through the dietary sources and nutritional supplements. The significance of ω -3 PUFAs on cardiometabolic is clear that is the reduction of inflammation agents that may contribute to metabolic syndrome as well as being essential in the prevention of cardiovascular diseases like thrombosis. Similarly, ω-6 PUFAs are important in the promotion of cardiovascular health by lowering cholesterol levels. Despite the highlighted benefits of the two fatty acids on cardiometabolic health, a significant controversy relates to the question as to whether ω-6 PUFAs contribute to inflammation or not. For instance, the conversion of SFA to PUFAs is always associated with a brisk of increasing inflammation. Omega 3- and 6 fatty acids have also been indicated to compete for substrates, and as a result, omega-3 is linked with anti-inflammatory behavior while omega-6 is linked with proinflammatory behavior. Also, the formation of omega-6 fatty acids is associated with the release of inflammatory molecules such as leukotrienes. The effect of downstream products produced by omega-3 and omega-6 fatty acids in relation to inflammation also remains unknown, while other studies suggest that inflammation linked to omega-6 could be explained by the highomega-3 to omega 6 ratios. Thus, there is a need to carry out more research on the link between omega-6 PUFAs and inflammation with specific emphasis being placed on the exact mechanism.

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