Review

Cardiovascular Diseases and Marine Oils: A Focus on Omega-3 Polyunsaturated Fatty Acids and Polar Lipids

Cliodhna Caffrey , Anna Leamy , Ellen O'Sullivan , Ioannis Zabetakis , Ronan Lordan , Constantina Nasopoulou *

Posted Date: 22 September 2023

doi: 10.20944/preprints202309.1538.v1

Keywords: Cardiovascular disease; Omega-3 polyunsaturated fatty acids; Polar lipids; Cardiovascular risk; Thrombosis; Platelet-activating factor (PAF); Eicosanoids; Resolvins; Fish oil

Review

Cardiovascular Diseases and Marine Oils: A Focus on Omega-3 Polyunsaturated Fatty Acids and Polar Lipids

Cliodhna Caffrey [1,†], Anna Leamy [1,†], Ellen O'Sullivan [1,†], Ioannis Zabetakis [1,2,3], Ronan Lordan [4,5,6] and Constantina Nasopoulou [7,*]

[1] Department of Biological Sciences, University of Limerick, Limerick, Ireland
[2] Health Research Institute (HRI), University of Limerick, Limerick, Ireland
[3] Bernal Institute, University of Limerick, Limerick, Ireland
[4] Institute for Translational Medicine and Therapeutics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, 19104, USA.
[5] Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, 19104, USA.
[6] Department of Systems Pharmacology and Therapeutics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, 19104, USA.
[7] Laboratory of Food Chemistry - Technology and Quality of Food of Animal Origin, Department of Food Science and Nutrition, University of the Aegean, Lemnos, Greece
* Correspondence: knasopoulou@aegean.gr .
† CC, AL and EOS contributed equally to this manuscript.

Abstract: Cardiovascular diseases (CVD) remain the leading cause of death across the globe, hence, establishing strategies to counteract CVD are imperative to reduce mortality and the burden on health systems. Dietary modification is an effective primary prevention strategy against CVD. Research regarding dietary supplementation has become increasingly popular. This review focuses on the current *in vivo*, *in vitro*, and epidemiological studies associated with that of omega-3 polyunsaturated fatty acids (n-3 PUFA) and polar lipids (PLs) and how they play a role against CVD. Furthermore, this review focuses on the results of several major clinical trials examining n-3 PUFA regarding both primary and secondary prevention of CVD. Notably, we place a lens on the REDUCE-IT and STRENGTH trials. Finally, supplementation of PLs has recently been suggested as a potential alternative avenue for the reduction of CVD incidence versus neutral forms of n-3 PUFA. However, the clinical evidence for this argument is currently rather limited. Therefore, we draw on the current literature to suggest future clinical trials for PL supplementation. We conclude that despite conflicting evidence, future human trials must be completed to confirm whether PL supplementation may be more effective than n-3 PUFA supplementation to reduce cardiovascular risk.

Keywords: cardiovascular disease; omega-3 polyunsaturated fatty acids; polar lipids; cardiovascular risk; thrombosis; platelet-activating factor (PAF); eicosanoids; resolvins; fish oil

1. Introduction

The burden of cardiovascular diseases (CVD) has lessened over the last two decades due to the development of novel therapies; however, such diseases maintain their status as the leading cause of death globally [1]. CVD has been reported to account for 1 in 4 deaths across Europe, and 1 in 3 deaths in the United States [2,3]. Diet is known to be one of the most important risk factors for CVD prevention and treatment [4,5]. A wide range of other traditional risk factors are also associated with CVD, namely, smoking, obesity, and lack of physical activity. A maladaptive lifestyle characterized by these risk factors can contribute to an increase in oxidative stress and inflammation, contributing to metabolic dysfunction and atherogenesis over time [6].

 doi:10.20944/preprints202309.1538.v1

Mechanistically, activated platelets play a major role in CVD [7–9]. Platelet activation, aggregation, and adhesion are all processes that contribute to the development of atherosclerosis over years potentially leading to vessel occlusion, the rupture of atherosclerotic lesions, and thrombosis, causing myocardial infarction, stroke, or other complications [10].

Evidence suggests that the consumption of foods or supplements containing marine oils may affect chronic diseases and complications of metabolic dysfunction such as atherosclerosis [11,12]. These include omega-3 polyunsaturated fatty acids (n-3 PUFA) and polar lipids (PLs). These lipids have been associated with the modulation of inflammatory and thrombotic pathways associated with atherogenesis [13].

The n-3 PUFA are a heterogenous group of fatty acids naturally present in algae, fish, shellfish, and other marine sources that can be harvested to produce supplements and nutraceuticals [14,15]. In nature, n-3 PUFA are most prevalent as neutral lipids (triglycerides, esters, etc.). However, they also present to a lesser extent in the form of PLs such as glycerophospholipids, glycolipids, and sphingolipids, which are amphipathic. PLs may increase the bioavailability of n-3 PUFA [16,17] and may exert cardioprotective effects independent of n-3 PUFA [18].

In this manuscript, we review of published research, reviews, and literature, to probe the role of n-3 PUFA and PL containing marine oils and their potential cardiovascular health benefits. We critically discuss crucial studies and trials that emerged from the literature, and we discuss the future of research in the field of marine oil cardioprotective products. In particular, we focus on the disparate results obtained in the REDUCE-IT and STRENGTH trials. Finally, we present a comparison of n-3 PUFA versus PL supplementation to identify evidence-based recommendations for conducting future clinical trials that may clarify and improve the current treatment and prevention strategies for both CVD and cardiovascular risk.

2. Marine Oils: Polyunsaturated Fatty Acids and Polar Lipids

In general, the consumption of supplements has increased over the past few decades due to increased consumer awareness and demand for wellness products [19]. Therefore, it is no surprise that the global nutraceuticals and supplements market was worth almost $353 billion USD in 2019 [20,21]. The consumption of marine oil supplements has steadily increased over the years due to their association with anti-inflammatory and cardioprotective effects relevant to public health [22]. Indeed, fish oils are the most commonly consumed dietary supplement aside from vitamin and mineral supplements in the US, whereby 7.8% and 1.1% of US adults and children respectively, consume fish oil supplements containing EPA, DHA, or a mix of n-3 PUFA [23,24]. In 2022, fish oil consumption globally reached 3.6 million metric tonnes [25]. In contrast, the projected fish oil production in 2010 was estimated to be only 1 million metric tonnes [26]. This phenomenal growth is expected to continue with the fish oil market expected to expand further at a compound annual growth rate of 5.9% from 2022 to 2030, valued at 3.62 billion USD [25]. However, the added value of producing supplement means the value is considerably higher, with global sale of omega 3 supplements generating approximately $5.18 billion in 2019 alone [27]. While this growth is largely driven by human consumption, fish oils are also used in animal and pet foods, cosmetics, aquaculture, and pharmaceuticals [25,26,28]. However, there have been reports that n-3 PUFA supplements often don't contain the correct amount of fatty n-3 PUFA or there is evidence of poor lipid quality or oxidation [29,30].

Despite their popularity among consumers, the scientific community is still at odds about the scientific evidence purporting cardioprotective effects in humans upon consumption. In this review, we discuss n-3 PUFA and PL marine oils and their potential cardiovascular effects.

2.1. n-3 PUFA Structure and Function

The n-3 PUFA have a double bond between the third and fourth carbon going from the end of the carbon chain (omega end), giving rise to the name n-3 PUFA. A short chain n-3 PUFA is considered to have a chain that consists of 18 carbons or under. A long chain n-3 PUFA has 20 or more carbons in its chain. Alpha-linolenic acid (ALA) is a common n-3 PUFA that is abundantly

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 22 September 2023 doi:10.20944/preprints202309.1538.v1

found in plant oils and the human diet, where it is found in soy, flaxseeds, and tree nuts in abundance (Figure 1). However, in marine oils the most abundant n-3 PUFA are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). EPA is a n-3 PUFA that comprises of a 20-carbon chain, making it a long chain n-3 PUFA, with five *cis* double bonds. The double bonds can be found at carbons 5, 8, 11,14, and 17. Docosahexaenoic acid (DHA) possesses a 22-carbon chain. Its structure contains six cis-double bonds located at carbons 4, 7, 10, 13, 16 and 19 [31–33] (Figure 1).

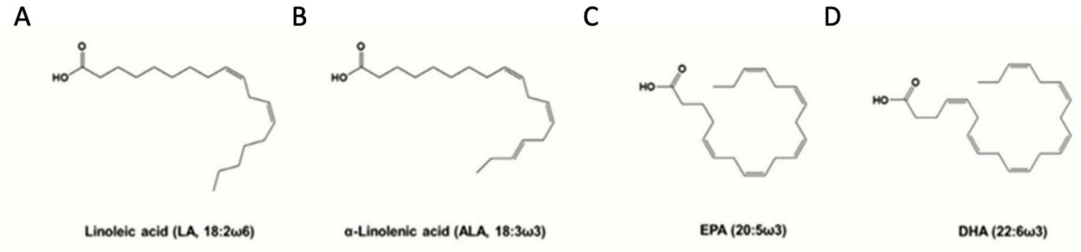

Figure 1. (a) Alpha-linoleic acid; (b) Eicosapentaenoic acid; (c) Docosahexaenoic acid. Adapted with permission from [34]. .

2.2. n-3 PUFA, Eicosapentaenoic Acid (EPA), and Docosahexaenoic Acid (DHA) and Cardiovascualr Health Effects

The efficacy of n-3 PUFA treatment of CVD has long been controversial. The n-3 PUFAs are known to be an essential element of the platelet phospholipid membrane. Hence, they play a vital role in platelet function and are studied fo their antiplatelet properties [35]. For over 20 years, supplementation of n-3 PUFA has been encouraged to curb the development of CVD [10]. While these supplements are voluntarily taken and prescribed for a wide range of medical conditions, they are predominately used for both the primary and secondary prevention of CVD [36].

The n-3 PUFA are known to have the ability to alter cell structure and cell signaling by altering the configuration of lipids within the cell membrane (Figure 2) [37]. This has been demonstrated by several animal studies that report that the alteration of cellular function can occur by the addition of n-3 PUFAs via the diet [38,39]. Incorporation of n-3 PUFAs into the cell membrane can also modulate ion channels, such as L-type calcium (Ca^{2+}) and sodium (Na^{+}) [40]. In addition, n-3 PUFAs may directly associate with both proteins and membrane channels (Figure 2). An example of this can be observed from the direct modulation of the G-protein-coupled receptor 120, or that of ion channels. Both actions have been noted to possibly aid in both anti-inflammatory and anti-arrhythmic responses associated with n-3 PUFA, respectively [41]. Figure 2 highlights how both transcription factors and nuclear receptors contribute to the regulation of gene expression, which is or course a direct result of the addition of n-3 PUFAs. As a whole, n-3 PUFAs are known to act as natural ligands of numerous nuclear receptors within various tissues of the body, such as liver X receptors and retinoid X receptors. The interactions between such nuclear receptors and that of n-3 PUFAs are altered by cytoplasmic lipid binding proteins, which in turn can carry the fatty acids inside the nucleus. N-3 PUFAs also amend the role of transcription factors, for example, the sterol regulatory element binding protein-1c. This regulation in turn plays a part in inflammatory pathways [42]. Figure 2 also highlights the conversion of n-3 PUFA from polar lipids in cell membranes to eicosanoids through three enzymes: lipoxygenase (LOX), cytochrome P450 (CYP450), and the cyclooxygenases (COX1 and COX2). Via incorporation into cell membranes, n-3 PUFA can supersede arachidonic acid (AA) and *hence, this* results in a reduction in AA-acquired eicosanoids [43]. This has been associated with a reduction of thrombosis, maladaptive vascular function, and inflammation.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 22 September 2023 doi:10.20944/preprints202309.1538.v1

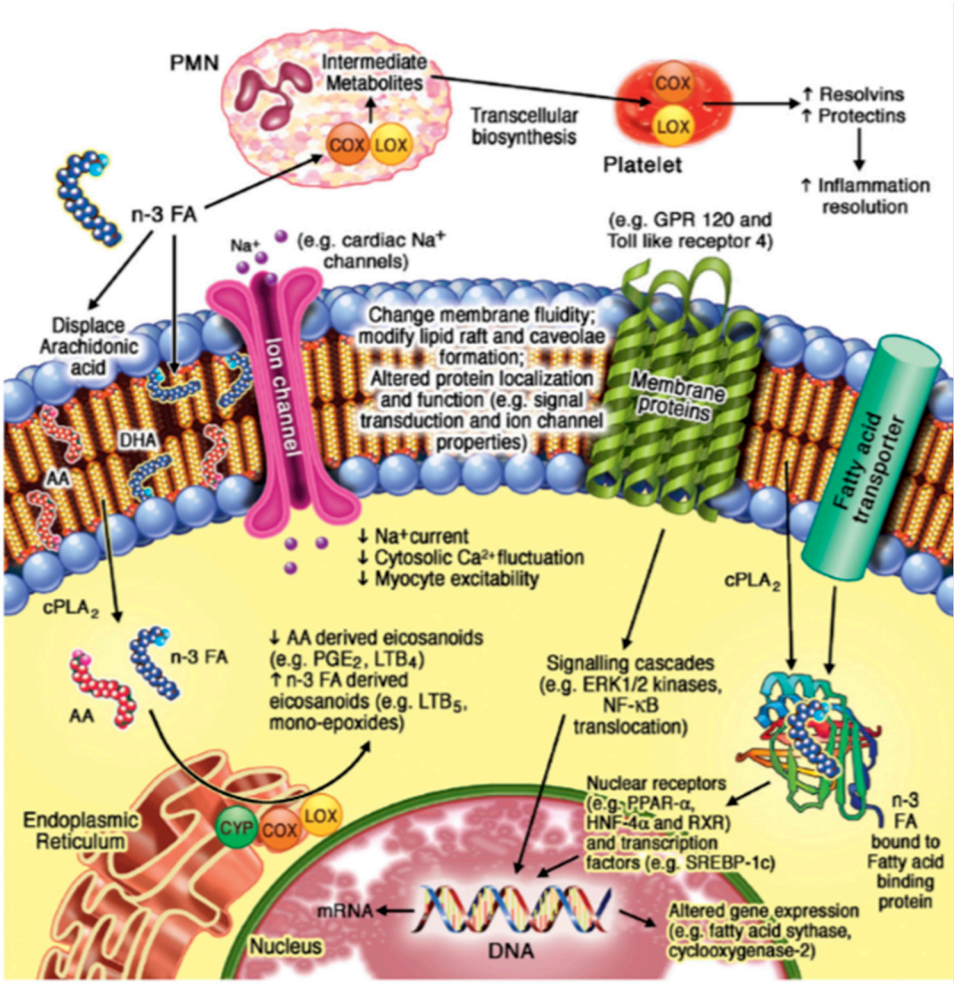

Figure 2. Hypothesized molecular effects of n-3 PUFA on the cell membrane. Reproduced with permission [1].

Another area of interest mechanistically has been the implication that n-3 PUFAs are required for the formation of specialized pro-resolving mediators (SPMs), involved in the so-called resolution of inflammation. A mechanism distinct from anti-inflammatory actions [44]. Such SPMs include protectins and resolvins, which are metabolites originating from the actions of the previously mentioned LOX and COX enzymes. It has been widely reported within animal models that n-3 PUFAs derived SPMs could possibly play a role in the reduction of chronic inflammation through the hypothesis of resolving inflammation [45]. However, evidence of these molecules exerting a beneficial effect in humans has been lacking [46,47] and the detection of resolvins in plasma and their functional relevance in human biology is an active but controversial field of research [48–51].

Both EPA and DHA appear to be the most functionally important n-3 PUFAs. Typically, they are both referred to as marine n-3 PUFAs due to their abundance in fatty (approx. 1-3.5g/serving) and lean fish (approx. 0.1-0.3g/serving), and other seafood. In addition, they are also found, although not equally, in various supplements. A summary of their relative concentrations of n-3 PUFA can be found in Table 1. In addition, examples of pharmaceutical grade EPA and DHA used within the industry are also detailed.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 22 September 2023 doi:10.20944/preprints202309.1538.v1

Table 1. A summary of EPA and DHA concentrations in various n-3 PUFA supplements. Data adapted with permission [52].

Supplements	n-3 PUFA content per gram of oil
Krill oil	205 mg
Tuna oil	460 mg
Fish oil (standard)	300 mg
Cod liver oil	200 mg
Algal oil	400 mg
Pharmaceuticals	**EPA/DHA content per gram of oil**
Omacor® (ethyl esters)	460mg (EPA) & 380mg (DHA)
Epanova® (carboxylic acids)	550mg (EPA) & 200mg (DHA)
Vascepa® (ethyl ester)	900 mg EPA

DHA and EPA exert a wide range of physiological effects including the reduction of triglycerides, heart rate, blood pressure, and platelet aggregation [18,22]. Both n-3 PUFAs also enhance arterial compliance and flow mediated dilation while also reducing pro-inflammatory cytokines and C-reactive protein (CRP) [53]. However, it has been consistently noted that such effects may be dependent on the specific health status or genetics of an individual [54–56], indicating that there may be a role for personalized nutrition and supplementation approaches [57]. EPA and DHA may also reduce plasma or serum concentrations of pro-inflammatory eicosanoids [58]. However, most research has focused on the use of EPA and DHA in combination, as opposed to their impact administered separately. EPA and DHA may exert differential effects on cardiovascular outcomes, particularly in lipid metabolism. Some of these effects including the reduction of inflammation and oxidation are summarised in Figure 3. However, the link between EPA and DHA in the modulation of inflammation lipoprotein metabolism has yet to be confirmed. Hence, currently there is no clear advantage between DHA and EPA for the modulation of lipid metabolism. However, it is likely a combination of both may yield the most advantageous health outcomes [59].

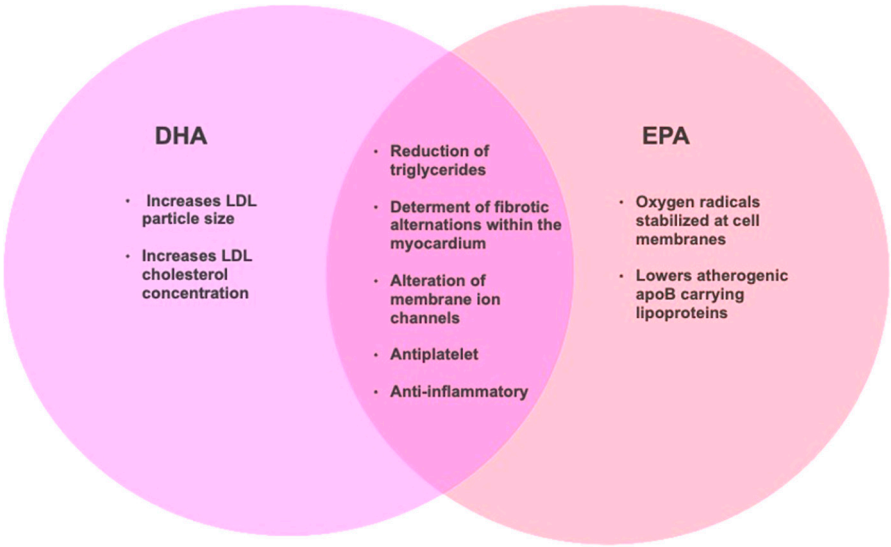

Figure 3. A summary of the potential benefits of DHA and EPA intake for cardiovascular health. Adapted with permission [60].

2.3. Polar Lipids Structure and Function

While the previous section focused on the neutral forms of n-3 PUFA including ethyl esters, triglyceride, and fatty acid forms; some n-3 PUFA are present as a constituent of PL (Figure 4). Preliminary evidence from nutritional studies suggests that PLs with/without n-3 PUFA in their structures may exert beneficial effects on CVD risk [61–64]. PLs are amphipathic molecules such as phospholipids or sphingolipids that are ubiquitous in nature. They are essential to the composition

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 22 September 2023 doi:10.20944/preprints202309.1538.v1

of cell membrane structure and function, cell signaling as secondary messengers, and lipid metabolism. They consist of a hydrophobic hydrocarbon tail and a polar hydrophilic head group [65]. Glycerophospholipids share a common assembly comprised of a glycerol backbone attached to a phosphate group and two fatty acids esterified to the *sn-1* and *sn*-2 positions. At the *sn*-3 position, the head group is comprised of a phosphate group and/or with phosphodiester linkages to organic molecules. These substituted head groups include choline (phosphatidylcholine), ethanolamine (phosphatidylethanolamine), serine (phosphatidylserine), or inositol (phosphatidylinositol). Sphingolipids replace the glycerol backbone with a sphingosine backbone, which is a long-chain amino alcohol that is amide-linked to the fatty acid and phosphate group [66,67]. Other common PLs include glycolipids and ceramides.

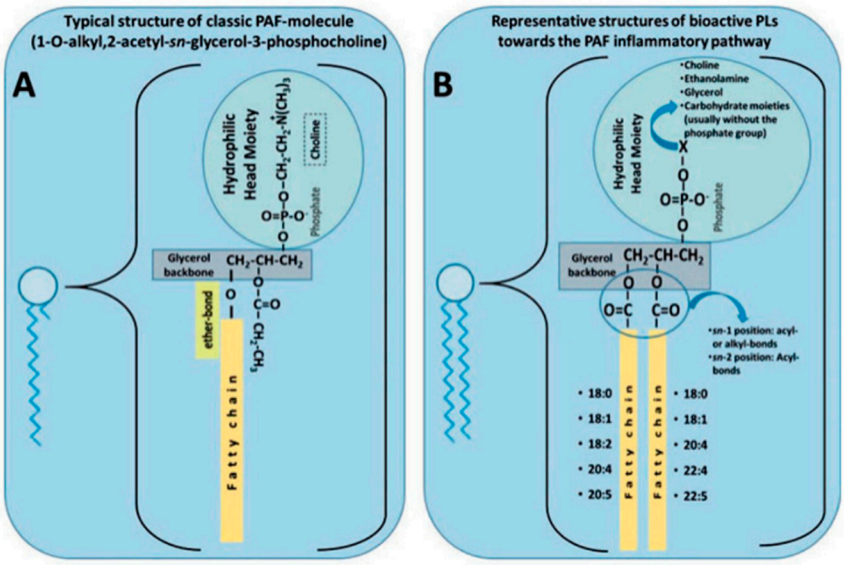

Figure 4. (A) The typical structure of a PAF molecule. (B) Representative structure of a bioactive polar lipid. Reproduced with permission [68].

2.4. Polar Lipids and Cardiovascular Health Effects

PLs are commonly found in foods such as olive oil, fish, meat, and dairy products associated with the Mediterranean diet [69,70]. The Mediterranean dietary pattern is strongly associated with a decreased risk of CVD [71] as demonstrated by the PREDIMED trials [72,73]. The Mediterranean diet has also been adopted outside of the Mediterranean region for the purpose of research, which appears to be a promising preventative and therapeutic option for CVD [74–76]. PLs are consumed in abundance as part of this dietary pattern. PLs have been postulated to be one of the constituents of the Mediterranean diet that may exert cardioprotective benefits via their antithrombotic and anti-inflammatory bioactivities against the actions of platelet-activating factor (PAF) and other inflammatory mediators [77–80]. PAF is a potent phospholipid mediator that interacts with its receptor (PAF-R) on the surface of numerous immune cells and platelets, causing platelet activation and pro-inflammatory cytokine release [81]. The production of PAF is stimulated by numerous cells such as platelets and leukocytes [82]. PAF is implicated in every stage of atherosclerosis through various mechanisms making it crucial to the process. The structure of PAF is characterised by an alkyl ether linkage, an acetyl group, and a phosphocholine group present at positions *sn*-1, *sn*-2, and *sn*-3 of the glycerol backbone, respectively [83]. PAF contributes to inflammation by mediating the adhesion of monocytes to the endothelium and in conjunction initiates gene transcription within monocytes resulting in the production of inflammatory cytokines. PAF generates an influx of Ca^{2+} ions, which increases endothelial permeability. This allows for the movement of LDL cholesterol and monocytes into the intima, allowing for the development of atherosclerotic plaque. Patients with CVD have elevated levels of PAF [84,85].

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 22 September 2023 doi:10.20944/preprints202309.1538.v1

However, PAF is an important regulator of various physiological functions. If unregulated, it can result in pro-inflammatory state leading to endothelial dysfunction and the development of atherosclerosis [69,81] (Figure 5). PAF and PAF-like molecules proceed via binding to a unique G protein-coupled receptor called PAF-receptor (PAF-R) [81]. PAF-R is expressed on platelets and is expressed by cells within the cardiovascular system. Ligand binding of PAF to the PAF-R provokes numerous intracellular signalling pathways which, if unregulated, can bring about a pro-inflammatory state, endothelial dysfunction, and the occurrence of atherosclerotic plaques [81].

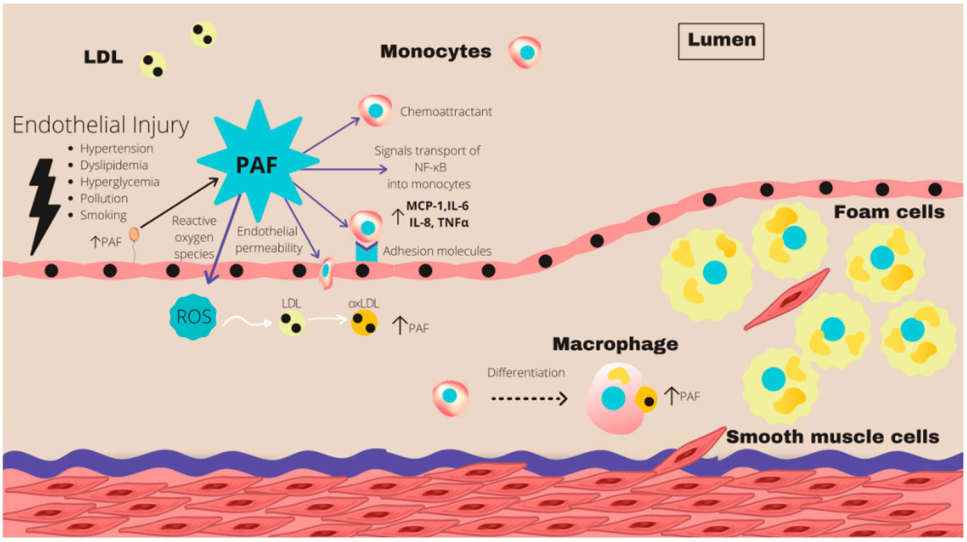

Figure 5. An illustration of the role of PAF in the initiation and progression of atherosclerotic plaque. Following exposure to injury, the endothelial cells are activated, triggering the synthesis of PAF and the expression of adhesion molecules, mediating the attachment of monocytes to the endothelium. PAF also triggers gene expression of pro-inflammatory cytokines such as IL-6 and TNF-α via NF-kB, and the production of ROS, which oxidizes LDL. PAF decreases the production of endothelial NO, increasing endothelial permeability. This allows for the movement of LDL and monocytes into the intima. PAF accounts for the polarization of monocytes into macrophages which engulf oxidized LDL, triggering the production of more PAF. Abbreviations: NF-kB, nuclear factor kB; IL, interleukin; PAF, platelet activating factor; TNF-α, tumour necrosis factor α; LDL, low density lipoprotein; ROS, reactive oxygen species.

Research suggests that PLs consumed in the diet are PAF antagonists that can inhibit PAF via their effects on the PAF receptor [81]. Indeed, some foods and natural products contain PAF antagonist [63]. This is due to the similarity in structure between PL and PAF/PAF-like molecules, examples of which include phospholipids and sphingolipids [69], as can be seen in Figure 4. It has also been suggested that PLs can modulate the metabolism of PAF [77,86,87]. As this is a newer area of research, evidence supporting these claims are lacking in human trials to date, but research continues [83].

2.5. Implications of Structural Differences Between n-3 PUFA and Polar Lipids

The n-3 PUFAs exist primarily esterified to triglycerides (neutral) or phospholipids (polar) in nature. Hydrolysis causes n-3 PUFAs to exist as free fatty acids (neutral). Structurally n-3 PUFA triglycerides differ to PLs as n-3 PUFA comprise of a glycerol backbone with 3 fatty acids attached to it. In contrast, PLs normally have two esterified fatty acids attached to the glycerol backbone as seen in Figure 4. PLs can form liposomes and micelles due to the differences in the physical-chemical structures between the structures [34]. PLs have an amphiphilic molecule which describes PLs to contain a hydrophobic tail and a hydrophilic head to occur naturally in these regions. This gives rise to PLs to act spontaneously as their hydrophilic region can attach to the aqueous phase and the

 doi:10.20944/preprints202309.1538.v1

hydrophobic region can attach to the non-aqueous phase where it is functionally able to be soluble in fat [35]. On the other hand, n-3 PUFAs triglycerides incur an exceedingly low water solubility which may have a negative effect on the utilization of n-3 PUFA supplements [36]. PLs are much more adverse with its bioactivity in comparison to n-3 PUFAs. As mentioned previously, PLs are found in the human diet as phospholipids and sphingolipids which are essential components of biological membranes [35]. Whereas n-3 PUFA are found in the body as ALA, DHA, and EPA as previously mentioned.

3. Marine Oils and Cardiovascular Health

3.1. Cardioprotective Marine Oil Supplements Containing n-3 PUFA and Polar lipids

Interest regarding marine oils grew from observations of the dietary patterns of Greenland Eskimos, who experienced a considerably lower incidence of cardiovascular disease attributed to their fatty fish-rich diet [52]. This has also been observed in Japanese populations where on average one fish meal per day is consumed providing approximately 900mg of n-3 PUFAs [88]. Research shows that consuming fatty fish as part of your weekly diet can significantly reduce the risk of CVD in comparison to a person that does not consume fish [89,90]. It is advised by the American Heart Association (AHA) to consume at least two meals containing fish per week. Fish consumption provides a wide array of dietary PUFA both in neutral and PL form that are generally not as easily acquired via supplementation [91]. Furthermore, there are additional benefits associated with consumption of the whole fish, including the addition of vitamins, minerals, and proteins. However, the AHA has recommended n-3 PUFA supplements if fresh fish is unavailable to meet recommended n-3 PUFA requirements and to reduce CVD risk [92,93]. However, the evidence regarding n-3 PUFA supplementation is not as straightforward and there are some inconsistencies regarding their role in both primary and secondary prevention of CVD. Indeed, large trials and meta-analyses have yielded inconsistent findings [94,95].

3.2. n-3 PUFA in clincial trials

Early trials conducted examining n-3 PUFA consumption focused on cardiovascular diseases, which largely concluded that n-3 PUFA were efficacious in the treatment and prevention of CVD. Therefore, there was general support for their consumption [96]. Examples of older trials that generally supported n-3 PUFA consumption to improve CVD risk include the Diet and Reinfarction Trial (DART), the Lyon Heart Study, and the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico Prevenzione tria (GISSI-P) [97,98]. However, due to limitations in these studies such as small sample sizes, the findings of these trials are often dismissed when examining the effects of n-3 PUFAs on CVD. With advances in cardiovascular knowledge, the results of many more recent randomised controlled trials (RCTs) have challenged previously recorded data [99,100]. More recently published studies are less encouraging regarding the importance of n-3 PUFAs and a reduction of CVD [100], and many studies are now focusing on alternative approaches including the delivery of n-3 PUFA in other forms such as PLs [18].

In recent years, there have been several large-scale trials that have examined the efficacy of n-3 PUFA supplementation. These include the REDUCE-IT trial and the STRENGTH trial. These trials were touted as the studies that may end the debate regarding n-3 PUFA and their cardioprotective effects. Therefore, in sections 3.2.1 and 3.2.2. we discuss the outcomes, strengths, and limitations of these trials and focus on how these studies have contributed to our growing knowledge regarding n-3 PUFA supplementation, cardiovascular health, and clinical trials.

3.2.1. The REDUCE-IT Trial in context

Icosapent ethyl (IPE), also known AMR101 or commercially as Vascepa®, is produced and marketed by the Irish company Amarin Pharma. IPE is a supplement composed of highly purified EPA. The product was initially approved by the United States Food and Drug Administration (FDA) for the treatment of hypertriglyceridemia [101]. The reduction of cardiovascular events with

 doi:10.20944/preprints202309.1538.v1

icosapent ethyl intervention trial (REDUCE-IT) was established to determine the potential of IPE to reduce ischemic events in patients diagnosed cardiovascular disease [102]. This was a major multicentre, double-blinded, randomised, placebo-controlled trial (mineral oil), which caused controversy between scientists and health experts since its publication [101]. Bhatt and colleagues enrolled over 8,000 patients with established cardiovascular disease or elevated risk, of which over 70% had experienced a previous cardiovascular event [103]. Participants were enrolled to the REDUCE-IT study if they were ≥ 45 years of age with previous CVD or if they were ≥ 50 years of age with diabetes and at least one other risk factor. These may include elevated fasting LDL levels, triglyceride levels, or patients receiving statin therapy. Patients were followed for a median of 4.9 years. The primary composite end points were cardiovascular mortality, nonfatal stroke, nonfatal myocardial infarction, unstable angina, or coronary revascularization.

Since the majority of the study population enrolled had established CVD, this study is generally viewed as a secondary prevention of CVD with n-3 PUFA supplementation study [104]. The results of the trial revealed that consumption of 2 g IPE *po bid* (4 g total per day) reduced the risk of ischemic cardiovascular events and death. Of those assigned to the IPE group, a primary endpoint occurred in 17.2 %, versus 22.0 % in the placebo group ($p < 0.001$; hazard ratio, 0.75; 95% confidence interval [CI], 0.068-0.83) or an absolute difference of 4.8%, irrespective of triglyceride levels at baseline or during the study [103]. Additional analyses supported that IPE supplementation may reduce CVD risk relating to high triglyceride levels [105]. Overall, IPE supplementation appeared to be safe with limited side effects including more frequent nonfatal adverse bleeding events, and more frequent hospitalization for peripheral oedema and atrial fibrillation in the IPE group versus the placebo group. [103,104].

While these widely anticipated results were well received initially, with the study being described as rounding the corner on residual risk [106], several concerns were raised regarding the study design. On closer inspection it was noted that the placebo mineral oil used for the trial was not inert, and that this may in fact have increased the placebo groups' risk for cardiovascular events. Indeed, the mineral oil intake was associated with an increase in LDL-C (7.4%), CRP (37.6%), and apolipoprotein B (6.7%) [103]. Similar increases in these biomarkers were reported as a consequence of mineral oil ingestion were previously reported in the ANCHOR [107] and MARINE [108] trials, which also investigated the use of IPE for cardiovascular risk reduction. In these studies, it is possible that the differences in the apparent reduction of cardiovascular risk associated with IPE treatment may be explained by the increased risk of exposure to mineral oil in the placebo group [101]. Although this is disputed in a review published by the REDUCE-IT trial authors [109]. Indeed, independent reviews by the FDA and other health agencies (Canada Health and the European Medicines Agency) concluded that the increases in these cardiovascular biomarkers associated with mineral oil may only partially explain the major cardiovascular events reported between the two randomized groups [101].

The data has not become any clearer since the trial was published. A meta-analysis of thirteen randomised controlled trials conducted by Hu *et al*. in 2019 concluded that consumption of marine n-3 PUFA supplementation does indeed lower the risk for myocardial infarction, both CHD total and death and also for both CVD total and death [110]. This meta-analysis also calculated the reduced risk excluding the REDUCE-IT trial due to the controversary surrounding its findings and still deduced that n-3 PUFA consumption was inversely associated with CVD. However, there were limitations to this study such as being unable to conduct subgroup analysis due to lack of study-level data available and the author does state that there is a need for additional large trials particularly those undertaken using high doses of n-3 PUFA supplementation to confirm and extend these findings. Another meta-analysis which was conducted by Shen *et al*. in 2022 found that additional n-3 PUFA supplementation may decrease the risk for incidence of major adverse cardiovascular events, cardiovascular death, and myocardial infarction [111]. However, the study also deduced that n-3 PUFA did not significantly impact all-cause death, stroke, and revascularisation. The study did however have minor limitations such as some subgroups containing a relatively low number of studies and more research is likely required to support and validate these findings.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 22 September 2023 doi:10.20944/preprints202309.1538.v1

In contrast, numerous studies failed to support the positive findings of the REDUCE-IT, JELIS, GISSI-P, and GISSI-HF (heart failure) trials [97,103,112,113]. These include trials such as VITAL (The VITamin D and OmegA-3 triaL), ORIGIN (Outcome Reduction with an Initial Glargine Intervention trial) and ASCEND (A Study of Cardiovascular Events in Diabetes) [114–116]. Collectively, these trials do not support the use of n-3 PUFA supplementation for cardioprotection against CVD. However, these trials differ in various aspects such as the placebo used, entry criteria, and the dosage of n-3 PUFA administered, which may account for the differences in the findings between these studies. Comparisons between some of these studies are presented in Table 2.

Table 2. Summary of investigations focusing on the effects of n-3 PUFAs on CVD in both healthy and high-risk patients.

Trial	*N*	Age	Formulation & Dose	Inclusion criteria/ cohort characteristics	Duration (Years)	Placebo
Successful – Primary endpoint reached*						
REDUCE-IT [103]	8,179	45 with CVD or 50 with DM	IPE 4 g	Patients with established CVD or DM on statin therapy with increased TG levels	4.9	Mineral oil
EVAPORATE [117]	80	30-85	IPE 4 g	Patients with confirmed coronary artery stenosis on statin therapy with increased TG levels.	1.5	Mineral oil
JELIS [112]	18,645	Men 40-75 Women up to 75 years	EPA 1.8 g + pravastatin or simvastatin	Patients with previous MI or PCI or with confirmed angina pectoris or without CVD.	4.6	No placebo
CHERRY [118]	193	67 10	Pivastatin + EPA 4 mg + 1800 mg	Patients with CHD after PCI	6-8 months	Pitavastatin 4 mg/day
Unsuccessful – Failed to reach primary endpoint*						
STRENGTH [119]	13,078	18-99 (>40 for men 50 for women if with DM)	EPA + DHA carboxylic acids 4 g	LDL-C < 100 mg/dL, on statins, TG levels 180-499 mg/dL, HDL-C < 42 mg/dL in men, <47mg/dL in women, patients with CVD or diabetes with risk factors.	5	Corn oil
VITAL [114]	25,871	Men > 50 Women > 55	EPA + DHA 1 g	Healthy men >50 and healthy women >55. TG levels not specified.	5.3	Not specified
ASCEND [116]	15,480	>40	EPA + DHA 1g	Persons older than 40 years with DM without CVD	7.4	Olive oil 1 g
ORIGIN [115]	12,536	50	EPA + DHA 465 mg + 375 mg	High risk of CVD + impaired fasting glucose/glucose intolerance/DM.	6.2	Olive oil 1 g
OMEMI [120]	1027	70-82 + Recent (2-8 weeks) MI	EPA + DHA 930 mg + 660 mg	Recent acute MI	2	Corn oil

* According to the study authors; Abbreviations = (IPE: icosapent ethyl, DM: diabetes metillus, TG: triglyceride, MI: mycocardial infarction, PCI: percutaneous coronary intervention).

3.2.2. The STRENGTH Trial in context

Epanova® was originally produced by Omthera Pharmaceuticals Inc. in New Jersey USA before being acquired by AstraZeneca. Epanova® is a 1 g supplement that delivers 850 mg of n-3 PUFA in the form of carboxylic acids. In the production process, the n-3 PUFA are hydrolysed and distilled from ethyl esters into PUFA carboxylic acids. The final concentration of EPA and DHA in this drug

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 22 September 2023 doi:10.20944/preprints202309.1538.v1

is 75%. The aim of this therapeutic was to maximize the EPA and DHA bioavailability for the treatment of hypertriglyceridemia. Epanova® does not need to be hydrolysed by lipases from the pancreas allowing easier absorption by the intestines and eliminating the need for consumption with a high-fat meal [121,122]. The STRENGTH trial was designed to examine the effects of Epanova® on reducing rates of cardiovascular events in statin-treated patients with hypertriglyceridemia [122]. STRENGTH involved a randomized, placebo-controlled, double-blind study between 13,078 patients in a 1:1 ratio treatment of 4g/day of n-3 PUFA carboxylic acids (Epanova®) versus 4 g/day of a corn oil placebo. Participants were 62.5 years consisting of 35% female participants. A corn oil placebo was chosen for this trial over mineral oil and liquid paraffin because it has a reduced incidence of gastrointestinal adverse effects and provides adequate calorie management. The criterion to participate for the STRENGTH trial included patients with high cardiovascular risk (CVR), determined atherosclerotic cardiovascular disease (ASCVD), established diabetes with an addition risk factor, or other high-risk primary prevention patients based on risk factor assessments and age factors, triglyceride levels ranging between 180 and 500mg/L, and high density-lipoprotein cholesterol (HDL-C) levels of < 42 mg/dL (men) or < 47 mg/dL(women) [119]. Additionally, participants were required to be on 100% statin therapy four weeks prior to the trial's commencement date and low-density lipoprotein cholesterol (LDL-C) levels had to be < 100 mg/dL [119,122].

The primary endpoints of the trial were the composite of cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke, unstable angina, and revascularization [119]. An interim analysis led to the early termination of the trial due to a perceived low clinical benefit of treatment versus the placebo. There were 1384 validated initial primary endpoint occurrences out of the predicted 1600 primary events among the almost 13,000 patients who completed the trial. In total, the primary endpoint occurred in 12% of the treated cohort (n = 785) versus 12.2% (n = 795) of the corn oil cohort. Furthermore, gastrointestinal adverse events occurred more frequently in the Epanova® group versus the corn oil cohort (24.7% versus 14.7% respectively). Likewise, atrial fibrilation was more frequently observed in the Epanova® group compared to the corn oil group (2.2% versus 1.3%) [119].

The addition of n-3 PUFA carboxylic acids to individuals on statin therapy with high cardiovascular risk compared to those on corn oil resulted in no meaningful change in a composite outcome of major adverse cardiovascular events. Therefore, the data reported does not support the use of this n-3 PUFA to reduce cardiovascular risk.

3.3. What Can We Learn from the STRENGTH and REDUCE-IT Trials

The role of n-3 PUFA supplementation and heart health strikes up great controversy due to heterogeneity between different clinical trials. This is clearly evident among some of the largest clinical trials. The most obvious examples include the more recent apparent successful reduction of cardiovascular risk observed in the REDUCE-IT trial and the apparent failure to reduce cardiovascular risk observed in the STRENGTH trial [123]. Some of these differences are presented in Table 3. There are several reasons why the results of these two important trials may differ.

Table 3. Comparisons between the STRENGTH and REDUCE-IT trials.

Clinical Trial	STRENGTH	REDUCE- IT
Number of participants	13078	8179
Population	High CVR, elevated TG levels, low HDL levels	High CVR, elevated TG levels, Diabetes
Treatment	DHA/EPA carboxylic acids (4g/d) (Epanova®)	Icosapent-ethyl ester (4g/d)
Placebo	Corn oil	Mineral oil
Follow-up Median	3.5 years	4.9 years
Primary Endpoint	Non-fatal stroke and MI, cardiovascular death, non-fatal	Non-fatal stroke and MI, cardiovascular

 doi:10.20944/preprints202309.1538.v1

	MI, coronary revascularization or unstable angina	death, coronary revascularization or unstable angina
95% CI of Primary Endpoint	0.99,0.90-1.09	0.75, 0.68-0.83

Abbreviations: CI = Confidence Interval.

To begin with, both trials opted to use different formulations of n-3 PUFA as previously alluded to. The REDUCE-IT trial provided participants with a 2 g dose of IPE (Vascepa) *po bid* or an equivalent style placebo containing mineral oil, participants were on a medically controlled 100% statin treatment [105]. Whereas the STRENGTH trial provided participants with Epanova® is a 1 g supplement that delivers 850 mg of n-3 PUFA in the form of carboxylic acids versus a corn oil placebo. While it is clear the type, form, and dosing of the n-3 PUFA differed between the trials. Another major difference is the absorption of the two products. IPE needs to be converted in the liver by hepatic conversion. In contrast, Epanova® is a carboxylic acid that has been exposed to additional manufacturing processes that allows the product to be consumed without the requirement of further hydrolyzation by pancreatic lipases [122]. This posed the question whether differing levels of bioavailability were at play. Indeed, higher serum EPA levels were measured in the REDUCE-IT cohort (144 µg/mL) versus the STRENGTH cohort (89 µg/mL) [124]. This is one potential reason for the observed disparity in findings between the trials. It was also questioned whether DHA may pose some harm in the STRENGTH trial, thus explaining the differing outcomes. However, a secondary analysis of the STRENGTH cohort indicated that there was no significant increase in benefit or any adverse outcomes in individuals with the highest levels of serum EPA or DHA [125].

As aforementioned, it is also important to acknowledge that the placebo used in both trials were different from each other, and this may indeed affect outcomes due to the potential negative effects of mineral oil on cardiovascular health [101,124]. Therefore, using mineral oil as a placebo may affect trial outcomes and raise the cardiovascular risk of those in the placebo group, falsely indicating a beneficial effect in the treatment group. However, these arguments are still being debated [101]. A cohort study using patients from the Copenhagen General Population Study (CGPS) was conducted to mimic the trial design of both studies to explain differences in observed CRP and serum lipid levels [126]. Patients who met the inclusion criteria took part in trial designs that emulated both the STRENGTH (n = 6862) and REDUCE-IT (n = 5684) studies. The authors of this study concluded that the contrasting results of both trials was likely due to a difference in the effect of the placebo oil used and not of the treatments assessed, as the mineral oil increased serum lipids and CRP [126]. However, this only partly explains the perceived benefit seen in the REDUCE-IT trial. Approximately, an additional 13% risk reduction may be due to a potential benefit of IPE, chance, or other factors [124]. Another way that both trials differed is in their enrollment criteria. While both trials needed patients with elevated lipid levels for study admission, REDUCE-IT only required mild hypertriglyceridemia (135 – 499 mg/dL) [103], whereas the STRENGTH trial required triglyceride levels between 180 and 500mg/dL [119]. While minor, differences in enrollment may bias trial outcomes.

Several n-3 PUFA products on the market are generally recognizedas safe (GRAS). However, both trials indicated that there was an increased incidence of atrial fibrillation among participants [124]. Therefore, at a popilation level, it is important that incidence of atrial fibrillation is continually monitored.

3.4. Marine Oil Polar Lipids and Human Health

The majority of fish oil products on the market are neutral n-3 PUFA products. PL products are less frequently available due to the loss of PL during the degumming processes conducted in industrial production of fish oil [127]. Although n-3 PUFA have been extensively studied for their potential health benefits, particularly in terms of CVD, PLs may be more effective as carriers of n-3 PUFA due to their increased bioavailability [16,18,127]. Krill oil is an example of a product, which contains a high proportion of n-3 PUFA bound to phospholipids [128,129]. The 72-hour bioavailability of 700mg DHA with EPA in krill oil was assessed in comparison to that of fish oil and krill meal within a randomized trial containing 15 healthy participants. In this study, when

 doi:10.20944/preprints202309.1538.v1

considering the primary endpoint, DHA along with EPA contained increased bioavailability in the krill oil sample compared to that of fish oil and krill meal. However, in terms of secondary endpoint, the results were conflicting. The bioavailability of the samples did not differ, which suggests that the phospholipids were not absorbed any better than that of the triglycerides [130,131]. Hence, further studies are ultimately required to confirm this hypothesis. In addition, a study undertaken by Lapointe, *et al.* [132] concluded that the bioavailability of the sample containing DHA and EPA in the form of that of PL esters was greater than that of the cohort containing n-3 PUFA in the ethyl ester form.

Marine PLs may counteract thrombosis and inflammation [18,133]. One study showed that oil extracts from fish such as sea bass, plaice, coley herring, rainbow and golden trout exhibited antiaggregatory properties against PAF-induced rabbit platelet aggregation *in vitro* [134]. All six fish are widely consumed in Europe. In a more recent study, fish oil obtained from salmon, herring, and boarfish, along with their processing by-products exhibited antithrombotic effects, against PAF and thrombin-induced human platelet aggregation due to their polar lipid content *in vitro*. Indeed, neutral lipids from the same fish did not exhibit the same level of antiplatelet activity despite their n-3 PUFA compositions [135]. Similar studies in human platelet aggregation studies against PAF and thrombin *in vitro* with salmon polar lipids [136] and food grade salmon polar lipids [137] have shown that marine oils rich in PL may exert favourable antiplatelet effects.

Fish fatty acid composition can change due to a variety of factors [138], and many researchers have shown that fish oil compositions change in response to diet alterations [139,140]. Food processing by-products are often used in animal feed. One such by-product is olive pomace (OP), which exhibited anti-PAF effects *in vitro* [141,142]. In one study, both sea bass (*Dicentrachus labrax*), and gilthead sea bream (*Sparus aurata*) were fed diets containing OP [143]. The results of this study indicated the PLs of the gilthead sea bream consisted of PAF inhibitors known to inhibit PAF both *in vivo* and *in vitro* likely accruing to a great extent due to the OP feed. However, incorporation of OP within fish feed at 8% appeared to negatively affect mortality and growth rate within sea bass, but a 4% OP diet was more tolerable. Oils obtained from these fish exhibited antiplatelet actions against PAF *in vitro*. To determine what lipids were responsible for the observed activity, Nasopoulou, *et al.* [144] isolated a number of lipid fractions to elucidate the structures and biological activity of the PL purported to be responsible for the cardioprotective activity observed *in vitro*. Seven lipid fractions extracted from the fish that consumed the OP diet exhibited potent inhibitory actions against PAF-induced platelet aggregation, in comparison with that of those fed with the conventional fish oil (FO) diet. Moreover, the balance of PL fractions of fish, which were consuming the OP diet resulted in a large increase in inhibitory activity against platelet aggregation as opposed to their respective PL fractions obtained from fish fed the FO diet. This likely suggests that antiplatelet properties of the OP were likely increased in the fish flesh and oils through the OP diet. Indeed, when the OP fed gilthead seabream (0.06%) fish oil was fed to hypercholesterolaemic rabbits, a reduction in plaque size was observed versus the cholesterol diet (1%) control rabbits, indicating a potential anti-atherosclerotic effect of the fish PL [145]. These affects may also in part be due to the observed modulation of PAF metabolic enzymes including PAF-acetylhydrolase (PAF-AH) both *in vitro* and *in vivo* [145,146]. When assessed in healthy human volunteers, OP-fed fish consumption did not significantly affect multiple cardiovascular markers with the exception of an elevated PAF-CPT (1-alkyl-2-acetyl-sn-glycerol-choline-phosphotransferase) and reduced arachidonic acid levels in red blood cells [147]. However, this study is still rather promising considering this was a healthy population. Further studies in patients with higher CVD risk may indicate whether consumption of such functional foods may benefit patient cardiovascular health. Collectively, these studies further highlight the role that both PAF and its metabolism play in atherosclerosis and the role that future fish PL-based therapeutics may play in the battle against CVD. Indeed, multiple studies have demonstrated potential antiplatelet properties of fish oil PL *in vitro* against PAF and various platelet agonists [135–137,148–150] and in various models of CVD *in vivo* [143,151]. However, it should be noted that PL sources characterised by lower levels of n-3 PUFA such as dairy and meat also exhibit antiplatelet

effects to a similar extent [152–154], indicating the promise of developing PL-based therapeutics generally.

A significant proportion of the n-3 PUFA composition of fish is obtained through dietary sources including microalgae, phytoplankton, and cyanobacteria [155]. Therefore, microalgae are becoming increasingly popular as a source of high value compounds with interesting bioactivity and chemical diversity. That said, the knowledge and understanding around their PLs' characteristics remains largely limited [156]. Algae contain lipids such as n-3 PUFA with antioxidant potential [157,158], which are sometimes attributed to the presence of glycolipids that are also known to exhibit antitumor and anti-inflammatory properties [159,160]. Indeed, it has been suggested to bypass the extraction of fish oil entirely and to instead focus on the production of n-3 PUFA supplements and nutraceuticals from microalgae as they are a source of high value lipids. Moreover, recent studies have suggested there is an abundance of therapeutic and pharmacological potential in relation to *Spirulina* biomass. Strong *in vitro* anti-thrombin and anti-PAF activities have been reported for extracts containing n-3 PUFA rich PL fractions of *Spirulina subsalsa* [161] and *Chlorococcum* sp [162]. Macroalgae are also under investigation for their PL composition. Both *Palmaria palmata* and *Grateloupia turuturu* are rich sources of EPA *Palmaria palmata* and PL extracts from these macroalgae exhibit antioxidant effect [163,164].

Despite this promising research, further investigation is required to establish these findings *in vivo*. More clinical trials are also required to further investigate PLs and their effects on cardiovascular health.

5. Conclusions and Future Research Directions

In this review, we investigated the evidence surrounding marine oil consumption and cardiovascular health. In particular, we focused on n-3 PUFA and PL supplementation and their capacity to reduce cardiovascular risk. In the n-3 PUFA research space, many large clinical trials have been conducted with variable results because of differing trial design, placebos used, doses, and the form of n-3 PUFA consumed. An in-depth review of the REDUCE-IT and Strength trials was conducted. Generally, while n-3 PUFA may provide some cardiovascular benefits, large scale trials have failed to conclusively support their use for cardiovascular risk reduction. This is largely due to differences in trial design, placebo use, and the different forms of n-3 PUFA that have been assessed. The consumption of n-3 PUFA supplements is high worldwide but likely poses limited risk for adverse events. Trials largely expressed concerns about the increased incidence of atrial fibrillation, which should be monitored closely at a population level. This review also evaluated the role and potential of n-3 PUFA withing dietary PLs and their potential cardiovascular benefits for risk reduction, through the examination of both *in vitro* and *in vivo* studies. Evidence regarding PL supplementation, although promising, is limited and further research is required. Given the large gaps within the literature remaining for both n-3 PUFAs and PLs, it is difficult to draw concrete conclusions. In designing future studies, we suggest that the form of n-3 PUFA used needs to be taken into account along with the choice of placebo. Studies investigating PL forms of n-3 PUFA are also warranted in humans to determine whether the polar head group conveys greater bioavailability of n-3 PUFA, thus increasing their efficacy and potency.

Author Contributions: Conceptualization, I.Z. and C.N.; methodology, C.C., A.L. and E.O.S.; software, C.C., A.L., E.O.S. and R.L.; validation, C.C., A.L., E.O.S. and I.Z.; formal analysis, C.C., A.L. and E.O.S.; investigation, C.C., A.L. and E.O.S.; resources, I.Z., C.N. and R.L.; data curation, X.X.; writing—original draft preparation, C.C., A.L., E.O.S. and R.L.; writing—review and editing, C.C., R.L., I.Z., and C.N.; visualization, R.L.; supervision, I.Z., C.N. and R.L.; project administration, I.Z., C.N. and R.L.; funding acquisition, I.Z. and C.N. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding. The APC was supported by Marine Drugs.

Institutional Review Board Statement: Not applicable

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Acknowledgments: We acknowledge the support of the Department of Biological Sciences, University of Limerick, Ireland.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Tsao, C.W.; Aday, A.W.; Almarzooq, Z.I.; Anderson, C.A.M.; Arora, P.; Avery, C.L.; Baker-Smith, C.M.; Beaton, A.Z.; Boehme, A.K.; Buxton, A.E., et al. Heart Disease and Stroke Statistics—2023 Update: A Report From the American Heart Association. *Circulation* **2023**, *147*, e93-e621, doi:doi:10.1161/CIR.0000000000001123.
2. Mozaffarian, D.; Wu, J.H.Y. Omega-3 Fatty Acids and Cardiovascular Disease: Effects on Risk Factors, Molecular Pathways, and Clinical Events. *Journal of the American College of Cardiology* **2011**, *58*, 2047-2067, doi:https://doi.org/10.1016/j.jacc.2011.06.063.
3. Ravera, A.; Carubelli, V.; Sciatti, E.; Bonadei, I.; Gorga, E.; Cani, D.; Vizzardi, E.; Metra, M.; Lombardi, C. Nutrition and Cardiovascular Disease: Finding the Perfect Recipe for Cardiovascular Health. *Nutrients* **2016**, *8*, 363.
4. Yu, E.; Malik, V.S.; Hu, F.B. Cardiovascular disease prevention by diet modification: JACC Health Promotion Series. *Journal of the American College of Cardiology* **2018**, *72*, 914-926, doi:doi:10.1016/j.jacc.2018.02.085.
5. Bhupathiraju, S.N.; Tucker, K.L. Coronary heart disease prevention: Nutrients, foods, and dietary patterns. *Clinica Chimica Acta* **2011**, *412*, 1493-1514, doi:https://doi.org/10.1016/j.cca.2011.04.038.
6. Manna, P.; Jain, S.K. Obesity, Oxidative Stress, Adipose Tissue Dysfunction, and the Associated Health Risks: Causes and Therapeutic Strategies. *Metab Syndr Relat Disord* **2015**, *13*, 423-444, doi:10.1089/met.2015.0095.
7. Stokes, K.Y.; Granger, D.N. Platelets: a critical link between inflammation and microvascular dysfunction. *The Journal of Physiology* **2012**, *590*, 1023-1034, doi:10.1113/jphysiol.2011.225417.
8. Lordan, R.; Tsoupras, A.; Zabetakis, I. Platelet activation and prothrombotic mediators at the nexus of inflammation and atherosclerosis: Potential role of antiplatelet agents. *Blood Rev.* **2020**, https://doi.org/10.1016/j.blre.2020.100694, 100694, doi:https://doi.org/10.1016/j.blre.2020.100694.
9. Aggarwal, A.; Jennings, C.L.; Manning, E.; Cameron, S.J. Platelets at the Vessel Wall in Non-Thrombotic Disease. *Circulation Research* **2023**, *132*, 775-790, doi:doi:10.1161/CIRCRESAHA.122.321566.
10. Adili, R.; Hawley, M.; Holinstat, M. Regulation of platelet function and thrombosis by omega-3 and omega-6 polyunsaturated fatty acids. *Prostaglandins & Other Lipid Mediators* **2018**, *139*, 10-18, doi:https://doi.org/10.1016/j.prostaglandins.2018.09.005.
11. Lordan, S.; Ross, R.P.; Stanton, C. Marine bioactives as functional food ingredients: potential to reduce the incidence of chronic diseases. *Marine drugs* **2011**, *9*, 1056-1100, doi:10.3390/md9061056.
12. Damaiyanti, D.W.; Tsai, Z.-Y.; Masbuchin, A.N.; Huang, C.-Y.; Liu, P.-Y. Interplay between fish oil, obesity and cardiometabolic diabetes. *Journal of the Formosan Medical Association* **2023**, *122*, 528-539, doi:https://doi.org/10.1016/j.jfma.2023.03.013.
13. Sunkara, A.; Raizner, A. Supplemental Vitamins and Minerals for Cardiovascular Disease Prevention and Treatment. *Methodist Debakey Cardiovasc J* **2019**, *15*, 179-184, doi:10.14797/mdcj-15-3-179.
14. Cholewski, M.; Tomczykowa, M.; Tomczyk, M. A Comprehensive Review of Chemistry, Sources and Bioavailability of Omega-3 Fatty Acids. *Nutrients* **2018**, *10*, 1662.
15. Vidal, N.P.; Dermiki, M.; Lordan, R. Chapter 11 - Fish-derived functional foods and cardiovascular health: An overview of current developments and advancements. In *Functional Foods and Their Implications for Health Promotion*, Zabetakis, I., Tsoupras, A., Lordan, R., Ramji, D., Eds. Academic Press: 2023; https://doi.org/10.1016/B978-0-12-823811-0.00002-Xpp. 303-316.
16. Burri, L.; Hoem, N.; Banni, S.; Berge, K. Marine omega-3 phospholipids: Metabolism and biological activities. *International Journal of Molecular Sciences* **2012**, *13*, 15401, doi:https://doi.org/10.3390/ijms131115401.
17. Cook, C.M.; Hallaråker, H.; Sæbø, P.C.; Innis, S.M.; Kelley, K.M.; Sanoshy, K.D.; Berger, A.; Maki, K.C. Bioavailability of long chain omega-3 polyunsaturated fatty acids from phospholipid-rich herring roe oil in men and women with mildly elevated triacylglycerols. *Prostaglandins, Leukotrienes and Essential Fatty Acids* **2016**, *111*, 17-24, doi:https://doi.org/10.1016/j.plefa.2016.01.007.

18. Lordan, R.; Redfern, S.; Tsoupras, A.; Zabetakis, I. Inflammation and cardiovascular disease: are marine phospholipids the answer? *Food Funct.* **2020**, *11*, 2861 - 2885, doi:https://doi.org/10.1039/C9FO01742A.
19. Chopra, A.S.; Lordan, R.; Horbańczuk, O.K.; Atanasov, A.G.; Chopra, I.; Horbańczuk, J.O.; Jóźwik, A.; Huang, L.; Pirgozliev, V.; Banach, M., et al. The current use and evolving landscape of nutraceuticals. *Pharma. Res.* **2022**, *175*, 106001, doi:https://doi.org/10.1016/j.phrs.2021.106001.
20. Lordan, R. Dietary supplements and nutraceuticals market growth during the coronavirus pandemic - Implications for consumers and regulatory oversight. *PharmaNutrition* **2021**, *18*, 100282, doi:10.1016/j.phanu.2021.100282.
21. Grand View Research. Nutraceuticals Market Analysis by Product (Dietary Supplements, Functional Food, Functional Beverage), By Region (North America, Asia Pacific, Europe, CSA, MEA), And Segment Forecasts, 2020 - 2027. . Availabe online: https://www.grandviewresearch.com/industry-analysis/nutraceuticals-market (accessed on 18 Aug).
22. Liao, J.; Xiong, Q.; Yin, Y.; Ling, Z.; Chen, S. The Effects of Fish Oil on Cardiovascular Diseases: Systematical Evaluation and Recent Advance. *Frontiers in Cardiovascular Medicine* **2022**, *8*, doi:10.3389/fcvm.2021.802306.
23. Clarke, T.C.; Black, L.I.; Stussman, B.J.; Barnes, P.M.; Nahin, R.L. Trends in the use of complementary health approaches among adults: United States, 2002-2012. *National Health Statistics Reports* **2015**, 1-16.
24. Black, L.I.; Clarke, T.C.; Barnes, P.M.; Stussman, B.J.; Nahin, R.L. Use of complementary health approaches among children aged 4-17 years in the United States: National Health Interview Survey, 2007-2012. *Natl Health Stat Report* **2015**, 1-19.
25. Grand view Research. Global Fish Oil Market is expected to value around US$ 3.62 Billion by 2030. Availabe online: https://www.globenewswire.com/news-release/2023/06/28/2696298/0/en/Global-Fish-Oil-Market-is-expected-to-value-around-US-3-62-Billion-by-2030.html (accessed on 18 Aug).
26. Pike, I.H.; Jackson, A. Fish oil: production and use now and in the future. *Lipid Technology* **2010**, *22*, 59-61, doi:https://doi.org/10.1002/lite.201000003.
27. Research, G.V. Omega 3 supplements market size & share report 2020-2027 Availabe online: https://www.grandviewresearch.com/industry-analysis/omega-3-supplement-market (accessed on 15 Aug).
28. Nasopoulou, C.; Zabetakis, I. Benefits of fish oil replacement by plant originated oils in compounded fish feeds. A review. *LWT-Food Science and Technology* **2012**, *47*, 217-224.
29. Pasini, F.; Gómez-Caravaca, A.M.; Blasco, T.; Cvejić, J.; Caboni, M.F.; Verardo, V. Assessment of Lipid Quality in Commercial Omega-3 Supplements Sold in the French Market. *Biomolecules* **2022**, *12*, 1361.
30. Albert, B.B.; Derraik, J.G.B.; Cameron-Smith, D.; Hofman, P.L.; Tumanov, S.; Villas-Boas, S.G.; Garg, M.L.; Cutfield, W.S. Fish oil supplements in New Zealand are highly oxidised and do not meet label content of n-3 PUFA. *Scientific Reports* **2015**, *5*, 7928, doi:10.1038/srep07928.
31. Zuliani, G.; Galvani, M.; Leitersdorf, E.; Volpato, S.; Cavalieri, M.; Fellin, R. The role of polyunsaturated fatty acids (PUFA) in the treatment of dyslipidemias. *Curr Pharm Des* **2009**, *15*, 4087-4093, doi:10.2174/138161209789909773.
32. Kones, R.; Howell, S.; Rumana, U. n-3 Polyunsaturated Fatty Acids and Cardiovascular Disease: Principles, Practices, Pitfalls, and Promises - A Contemporary Review. *Med Princ Pract* **2017**, *26*, 497-508, doi:10.1159/000485837.
33. Kaur, N.; Chugh, V.; Gupta, A.K. Essential fatty acids as functional components of foods- a review. *J Food Sci Technol* **2014**, *51*, 2289-2303, doi:10.1007/s13197-012-0677-0.
34. Huang, T.-H.; Wang, P.-W.; Yang, S.-C.; Chou, W.-L.; Fang, J.-Y. Cosmetic and therapeutic applications of fish oil's fatty acids on the skin. *Marine Drugs* **2018**, *16*, 256.
35. Yamaguchi, A.; Stanger, L.; Freedman, J.C.; Prieur, A.; Thav, R.; Tena, J.; Holman, T.R.; Holinstat, M. Supplementation with omega-3 or omega-6 fatty acids attenuates platelet reactivity in postmenopausal women. *Clinical and Translational Science* **2022**, *15*, 2378-2391, doi:https://doi.org/10.1111/cts.13366.
36. Nevigato, T.; Masci, M.; Caproni, R. Quality of Fish-Oil-Based Dietary Supplements Available on the Italian Market: A Preliminary Study. *Molecules* **2021**, *26*, doi:10.3390/molecules26165015.
37. Kaur, G.; Malik, R.K.; Mishra, S.K.; Singh, T.P.; Bhardwaj, A.; Singroha, G.; Vij, S.; Kumar, N. Nisin and Class IIa Bacteriocin Resistance Among Listeria and Other Foodborne Pathogens and Spoilage Bacteria. *Microbial Drug Resistance* **2011**, *17*, 197-205, doi:10.1089/mdr.2010.0054.

38. Duda, M.K.; O'Shea, K.M.; Tintinu, A.; Xu, W.; Khairallah, R.J.; Barrows, B.R.; Chess, D.J.; Azimzadeh, A.M.; Harris, W.S.; Sharov, V.G., et al. Fish oil, but not flaxseed oil, decreases inflammation and prevents pressure overload-induced cardiac dysfunction. *Cardiovasc Res* **2009**, *81*, 319-327, doi:10.1093/cvr/cvn310.
39. Teng, L.L.; Shao, L.; Zhao, Y.T.; Yu, X.; Zhang, D.F.; Zhang, H. The beneficial effect of n-3 polyunsaturated fatty acids on doxorubicin-induced chronic heart failure in rats. *J Int Med Res* **2010**, *38*, 940-948, doi:10.1177/147323001003800320.
40. Drenjančević, I.; Pitha, J. Omega-3 Polyunsaturated Fatty Acids-Vascular and Cardiac Effects on the Cellular and Molecular Level (Narrative Review). *Int J Mol Sci* **2022**, *23*, doi:10.3390/ijms23042104.
41. Oh, D.Y.; Talukdar, S.; Bae, E.J.; Imamura, T.; Morinaga, H.; Fan, W.; Li, P.; Lu, W.J.; Watkins, S.M.; Olefsky, J.M. GPR120 is an omega-3 fatty acid receptor mediating potent anti-inflammatory and insulin-sensitizing effects. *Cell* **2010**, *142*, 687-698, doi:10.1016/j.cell.2010.07.041.
42. Adkins, Y.; Kelley, D.S. Mechanisms underlying the cardioprotective effects of omega-3 polyunsaturated fatty acids. *J Nutr Biochem* **2010**, *21*, 781-792, doi:10.1016/j.jnutbio.2009.12.004.
43. Cottin, S.C.; Sanders, T.A.; Hall, W.L. The differential effects of EPA and DHA on cardiovascular risk factors. *Proceedings of the Nutrition Society* **2011**, *70*, 215-231, doi:10.1017/S0029665111000061.
44. Serhan, C.N.; Chiang, N.; Van Dyke, T.E. Resolving inflammation: dual anti-inflammatory and pro-resolution lipid mediators. *Nature reviews. Immunology* **2008**, *8*, 349-361, doi:10.1038/nri2294.
45. Serhan, C.N. Novel lipid mediators and resolution mechanisms in acute inflammation: to resolve or not? *Am J Pathol* **2010**, *177*, 1576-1591, doi:10.2353/ajpath.2010.100322.
46. Skarke, C.; Alamuddin, N.; Lawson, J.A.; Li, X.; Ferguson, J.F.; Reilly, M.P.; FitzGerald, G.A. Bioactive products formed in humans from fish oils. *Journal of Lipid research* **2015**, *56*, 1808-1820.
47. Lordan, R.; Tsoupras, A.; Zabetakis, I. Platelet activation and prothrombotic mediators at the nexus of inflammation and atherosclerosis: Potential role of antiplatelet agents. *Blood Reviews* **2021**, *45*, 100694, doi:https://doi.org/10.1016/j.blre.2020.100694.
48. Schebb, N.H.; Kühn, H.; Kahnt, A.S.; Rund, K.M.; O'Donnell, V.B.; Flamand, N.; Peters-Golden, M.; Jakobsson, P.J.; Weylandt, K.H.; Rohwer, N., et al. Formation, Signaling and Occurrence of Specialized Pro-Resolving Lipid Mediators-What is the Evidence so far? *Front Pharmacol* **2022**, *13*, 838782, doi:10.3389/fphar.2022.838782.
49. O'Donnell, V.; Schebb, N.; Milne, G.; Murphy, M.; Thomas, C.; Steinhilber, D.; Wendell, S.; Kühn, H.; Jakobsson, P.; Blair, I. Failure to apply standard limit-of-detection or limit-of-quantitation criteria to specialized pro-resolving mediator analysis incorrectly characterizes their presence in biological samples. *Zenodo* **2021**, *1*, 10.5281.
50. Kahnt, A.S.; Schebb, N.H.; Steinhilber, D. Formation of lipoxins and resolvins in human leukocytes. *Prostaglandins Other Lipid Mediat* **2023**, *166*, 106726, doi:10.1016/j.prostaglandins.2023.106726.
51. Sinha, G. Critics Challenge Data showing key lipids can curb inflammation *Science* **2022**, https://doi.org/10.1126/science.abq8439, doi:https://doi.org/10.1126/science.abq8439.
52. Innes, J.K.; Calder, P.C. Marine Omega-3 (N-3) Fatty Acids for Cardiovascular Health: An Update for 2020. *International Journal of Molecular Sciences* **2020**, *21*, 1362.
53. AbuMweis, S.; Jew, S.; Tayyem, R.; Agraib, L. Eicosapentaenoic acid and docosahexaenoic acid containing supplements modulate risk factors for cardiovascular disease: a meta-analysis of randomised placebo-control human clinical trials. *Journal of Human Nutrition and Dietetics* **2018**, *31*, 67-84, doi:10.1111/jhn.12493.
54. Grimble, R.F.; Howell, W.M.; O'Reilly, G.; Turner, S.J.; Markovic, O.; Hirrell, S.; East, J.M.; Calder, P.C. The ability of fish oil to suppress tumor necrosis factor alpha production by peripheral blood mononuclear cells in healthy men is associated with polymorphisms in genes that influence tumor necrosis factor alpha production. *Am J Clin Nutr* **2002**, *76*, 454-459, doi:10.1093/ajcn/76.2.454.
55. Rundblad, A.; Sandoval, V.; Holven, K.B.; Ordovás, J.M.; Ulven, S.M. Omega-3 fatty acids and individual variability in plasma triglyceride response: A mini-review. *Redox Biology* **2023**, *63*, 102730, doi:https://doi.org/10.1016/j.redox.2023.102730.
56. Minihane, A.M. Impact of Genotype on EPA and DHA Status and Responsiveness to Increased Intakes. *Nutrients* **2016**, *8*, 123, doi:10.3390/nu8030123.
57. Troesch, B.; Eggersdorfer, M.; Laviano, A.; Rolland, Y.; Smith, A.D.; Warnke, I.; Weimann, A.; Calder, P.C. Expert Opinion on Benefits of Long-Chain Omega-3 Fatty Acids (DHA and EPA) in Aging and Clinical Nutrition. *Nutrients* **2020**, *12*, doi:10.3390/nu12092555.

58. Xin, W.; Wei, W.; Li, X.Y. Short-term effects of fish-oil supplementation on heart rate variability in humans: a meta-analysis of randomized controlled trials. *Am J Clin Nutr* **2013**, *97*, 926-935, doi:10.3945/ajcn.112.049833.
59. Innes, K.J.; Calder, C.P. The Differential Effects of Eicosapentaenoic Acid and Docosahexaenoic Acid on Cardiometabolic Risk Factors: A Systematic Review. *International Journal of Molecular Sciences* **2018**, *19*, doi:10.3390/ijms19020532.
60. Jacobson, T.A.; Glickstein, S.B.; Rowe, J.D.; Soni, P.N. Effects of eicosapentaenoic acid and docosahexaenoic acid on low-density lipoprotein cholesterol and other lipids: A review. *Journal of Clinical Lipidology* **2012**, *6*, 5-18, doi:https://doi.org/10.1016/j.jacl.2011.10.018.
61. Vors, C.; Joumard-Cubizolles, L.; Lecomte, M.; Combe, E.; Ouchchane, L.; Drai, J.; Raynal, K.; Joffre, F.; Meiller, L.; Le Barz, M., et al. Milk polar lipids reduce lipid cardiovascular risk factors in overweight postmenopausal women: towards a gut sphingomyelin-cholesterol interplay. *Gut* **2020**, *69*, 487-501, doi:10.1136/gutjnl-2018-318155.
62. Hossain, M.M.; Tovar, J.; Cloetens, L.; Florido, M.T.S.; Petersson, K.; Prothon, F.; Nilsson, A. Oat Polar Lipids Improve Cardiometabolic-Related Markers after Breakfast and a Subsequent Standardized Lunch: A Randomized Crossover Study in Healthy Young Adults. *Nutrients* **2021**, *13*, 988.
63. Antonopoulou, S.; Detopoulou, M.; Fragopoulou, E.; Nomikos, T.; Mikellidi, A.; Yannakoulia, M.; Kyriacou, A.; Mitsou, E.; Panagiotakos, D.; Anastasiou, C. Consumption of yogurt enriched with polar lipids from olive oil by-products reduces platelet sensitivity against platelet activating factor and inflammatory indices: A randomized, double-blind clinical trial. *Human Nutr. Metab.* **2022**, *28*, 200145, doi:https://doi.org/10.1016/j.hnm.2022.200145.
64. Le Barz, M.; Vors, C.; Combe, E.; Joumard-Cubizolles, L.; Lecomte, M.; Joffre, F.; Trauchessec, M.; Pesenti, S.; Loizon, E.; Breyton, A.-E. Milk polar lipids favorably alter circulating and intestinal ceramide and sphingomyelin species in postmenopausal women. *JCI insight* **2021**, *6*, doi:https://doi.org/10.1172/jci.insight.146161.
65. Lordan, R.; Tsoupras, A.; Zabetakis, I. Phospholipids of animal and marine origin: Structure, function, and anti-inflammatory properties. *Molecules* **2017**, *22*, 1964, doi:https://doi.org/10.3390/molecules22111964
66. Anto, L.; Warykas, S.W.; Torres-Gonzalez, M.; Blesso, C.N. Milk polar lipids: Underappreciated lipids with emerging health benefits. *Nutrients* **2020**, *12*, 1001, doi:https://doi.org/10.3390/nu12041001.
67. Lordan, R.; Blesso, C.N. Editorial: Phospholipids and sphingolipids in nutrition, metabolism, and health. *Front. Nutr.* **2023**, *10*, doi:https://doi.org/10.3389/fnut.2023.1153138.
68. Lordan, R.; Zabetakis, I.; Tsoupras, A. Inflammation and Chronic Diseases: The Polar Lipid Link. *Proceedings* **2021**, *70*, 70.
69. Tsoupras, A.; Lordan, R.; Zabetakis, I. Inflammation, not cholesterol, is a cause of chronic disease. *Nutrients* **2018**, *10*, 604, doi:doi:10.3390/nu10050604
70. Zheng, L.; Fleith, M.; Giuffrida, F.; O'Neill, B.V.; Schneider, N. Dietary Polar Lipids and Cognitive Development: A Narrative Review. *Adv Nutr* **2019**, *10*, 1163-1176, doi:10.1093/advances/nmz051.
71. Martínez-González, M.A.; Salas-Salvadó, J.; Estruch, R.; Corella, D.; Fitó, M.; Ros, E. Benefits of the Mediterranean Diet: Insights From the PREDIMED Study. *Prog Cardiovasc Dis* **2015**, *58*, 50-60, doi:https://doi.org/10.1016/j.pcad.2015.04.003.
72. Estruch, R.; Martinez-Gonzalez, M.A.; Corella, D.; Salas-Salvado, J.; Ruiz-Gutierrez, V.; Covas, M.I.; Fiol, M.; Gomez-Gracia, E.; Lopez-Sabater, M.C.; Vinyoles, E., et al. Effects of a Mediterranean-style diet on cardiovascular risk factors: a randomized trial. *Annals of Internal Medicine* **2006**, *145*, 1-11.
73. Estruch, R.; Ros, E.; Salas-Salvadó, J.; Covas, M.-I.; Corella, D.; Arós, F.; Gómez-Gracia, E.; Ruiz-Gutiérrez, V.; Fiol, M.; Lapetra, J., et al. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. *New England Journal of Medicine* **2018**, *0*, null, doi:10.1056/NEJMoa1800389.
74. Tognon, G.; Nilsson, L.M.; Lissner, L.; Johansson, I.; Hallmans, G.; Lindahl, B.; Winkvist, A. The Mediterranean diet score and mortality are inversely associated in adults living in the subarctic region. *Journal of Nutrition* **2012**, *142*, 1547-1553, doi:10.3945/jn.112.160499.
75. Mayr, H.L.; Itsiopoulos, C.; Tierney, A.C.; Ruiz-Canela, M.; Hebert, J.R.; Shivappa, N.; Thomas, C.J. Improvement in dietary inflammatory index score after 6-month dietary intervention is associated with reduction in interleukin-6 in patients with coronary heart disease: The AUSMED heart trial. *Nutrition Research* **2018**, *55*, 108-121, doi:https://doi.org/10.1016/j.nutres.2018.04.007.

76. Mayr, H.L.; Tierney, A.C.; Kucianski, T.; Thomas, C.J.; Itsiopoulos, C. Australian patients with coronary heart disease achieve high adherence to 6-month Mediterranean diet intervention: preliminary results of the AUSMED Heart Trial. *Nutrition* **2018**, https://doi.org/10.1016/j.nut.2018.10.027, doi:https://doi.org/10.1016/j.nut.2018.10.027.
77. Lordan, R.; Nasopoulou, C.; Tsoupras, A.; Zabetakis, I. The anti-inflammatory properties of food polar lipids. In *Bioactive Molecules in Food*, Mérillon, J.M., Ramawat, K.G., Eds. Springer International Publishing: Cham, Switzerland, 2018; doi:10.1007/978-3-319-54528-8_95-1pp. 1-34.
78. Nomikos, T.; Fragopoulou, E.; Antonopoulou, S.; Panagiotakos, D.B. Mediterranean diet and platelet-activating factor; a systematic review. *Clinical Biochemistry* **2018**, https://doi.org/10.1016/j.clinbiochem.2018.08.004, doi:https://doi.org/10.1016/j.clinbiochem.2018.08.004.
79. Detopoulou, P.; Demopoulos, C.; Karantonis, H.; Antonopoulou, S. Mediterranean diet and its protective mechanisms against cardiovascular disease: An insight into Platelet Activating Factor (PAF) and diet interplay. *Ann Nutr Disord Ther* **2015**, *2*, 1-10.
80. Demopoulos, C.A.; Karantonis, H.C.; Antonopoulou, S. Platelet-activating factor — a molecular link between atherosclerosis theories. *European Journal of Lipid Science and Technology* **2003**, *105*, 705-716, doi:http://dx.doi.org/10.1002/ejlt.200300845.
81. Harishkumar, R.; Hans, S.; Stanton, J.E.; Grabrucker, A.M.; Lordan, R.; Zabetakis, I. Targeting the Platelet-Activating Factor Receptor (PAF-R): Antithrombotic and Anti-Atherosclerotic Nutrients. *Nutrients* **2022**, *14*, 4414, doi:https://doi.org/10.3390/nu14204414.
82. English, C.J.; Mayr, H.L.; Lohning, A.E.; Reidlinger, D.P. The association between dietary patterns and the novel inflammatory markers platelet-activating factor and lipoprotein-associated phospholipase A2: a systematic review. *Nutr Rev* **2022**, *80*, 1371-1391, doi:10.1093/nutrit/nuab051.
83. Lordan, R.; Tsoupras, A.; Zabetakis, I.; Demopoulos, A.C. Forty years since the structural elucidation of platelet-activating factor (PAF): Historical, current, and future research perspectives. *Molecules* **2019**, *24*, doi:doi:10.3390/molecules24234414.
84. English, C.J.; Mayr, H.L.; Lohning, A.E.; Reidlinger, D.P. The association between dietary patterns and the novel inflammatory markers platelet-activating factor and lipoprotein-associated phospholipase A2: a systematic review. *Nutrition Reviews* **2022**, *80*, 1371-1391, doi:10.1093/nutrit/nuab051.
85. Palur Ramakrishnan, A.V.K.; Varghese, T.P.; Vanapalli, S.; Nair, N.K.; Mingate, M.D. Platelet activating factor: A potential biomarker in acute coronary syndrome? *Cardiovascular Therapeutics* **2017**, *35*, 64-70, doi:https://doi.org/10.1111/1755-5922.12233.
86. Detopoulou, M.; Ntzouvani, A.; Petsini, F.; Gavriil, L.; Fragopoulou, E.; Antonopoulou, S. Consumption of Enriched Yogurt with PAF Inhibitors from Olive Pomace Affects the Major Enzymes of PAF Metabolism: A Randomized, Double Blind, Three Arm Trial. *Biomolecules* **2021**, *11*, doi:https://doi.org/10.3390/biom11060801.
87. Argyrou, C.; Vlachogianni, I.; Stamatakis, G.; Demopoulos, C.A.; Antonopoulou, S.; Fragopoulou, E. Postprandial effects of wine consumption on Platelet Activating Factor metabolic enzymes. *Prostaglandins & Other Lipid Mediators* **2017**, http://dx.doi.org/10.1016/j.prostaglandins.2017.03.002, doi:http://dx.doi.org/10.1016/j.prostaglandins.2017.03.002.
88. Meyer, B.; Groot, R. Effects of Omega-3 Long Chain Polyunsaturated Fatty Acid Supplementation on Cardiovascular Mortality: The Importance of the Dose of DHA. *Nutrients* **2017**, *9*, 1305.
89. Chaddha, A.; Eagle, K.A. Omega-3 Fatty Acids and Heart Health. *Circulation* **2015**, *132*, e350-e352, doi:doi:10.1161/CIRCULATIONAHA.114.015176.
90. Stone, N.J. Fish Consumption, Fish Oil, Lipids, and Coronary Heart Disease. *Circulation* **1996**, *94*, 2337-2340, doi:doi:10.1161/01.CIR.94.9.2337.
91. Weichselbaum, E.; Coe, S.; Buttriss, J.; Stanner, S. Fish in the diet: A review. *Nutrition Bulletin* **2013**, *38*, 128-177, doi:https://doi.org/10.1111/nbu.12021.
92. Lichtenstein, A.H.; Appel, L.J.; Vadiveloo, M.; Hu, F.B.; Kris-Etherton, P.M.; Rebholz, C.M.; Sacks, F.M.; Thorndike, A.N.; Horn, L.V.; Wylie-Rosett, J. 2021 Dietary Guidance to Improve Cardiovascular Health: A Scientific Statement From the American Heart Association. *Circulation* **2021**, *144*, e472-e487, doi:doi:10.1161/CIR.0000000000001031.
93. Rimm, E.B.; Appel, L.J.; Chiuve, S.E.; Djoussé, L.; Engler, M.B.; Kris-Etherton, P.M.; Mozaffarian, D.; Siscovick, D.S.; Lichtenstein, A.H. Seafood Long-Chain n-3 Polyunsaturated Fatty Acids and

Cardiovascular Disease: A Science Advisory From the American Heart Association. *Circulation* **2018**, *138*, e35-e47, doi:doi:10.1161/CIR.0000000000000574.

94. Kwak, S.; Myung, S.; Lee, Y.; Seo, H.; Korean Meta-analysis Study Group, f. Efficacy of omega-3 fatty acid supplements (eicosapentaenoic acid and docosahexaenoic acid) in the secondary prevention of cardiovascular disease: A meta-analysis of randomized, double-blind, placebo-controlled trials. *Archives of Internal Medicine* **2012**, *172*, 686-694, doi:10.1001/archinternmed.2012.262.
95. Abdelhamid, A.S.; Brown, T.J.; Brainard, J.S.; Biswas, P.; Thorpe, G.C.; Moore, H.J.; Deane, K.H.O.; AlAbdulghafoor, F.K.; Summerbell, C.D.; Worthington, H.V., et al. Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease. *Cochrane Database of Systematic Reviews* **2018**, 10.1002/14651858.CD003177.pub4, doi:10.1002/14651858.CD003177.pub4.
96. Bowen, K.J.; Harris, W.S.; Kris-Etherton, P.M. Omega-3 Fatty Acids and Cardiovascular Disease: Are There Benefits? *Current Treatment Options in Cardiovascular Medicine* **2016**, *18*, 69, doi:10.1007/s11936-016-0487-1.
97. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. *Lancet* **1999**, *354*, 447-455, doi:https://doi.org/10.1016/S0140-6736(99)07072-5.
98. De Lorgeril, M.; Renaud, S.; Salen, P.; Monjaud, I.; Mamelle, N.; Martin, J.; Guidollet, J.; Touboul, P.; Delaye, J. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. *The Lancet* **1994**, *343*, 1454-1459.
99. Maehre, H.K.; Jensen, I.J.; Elvevoll, E.O.; Eilertsen, K.E. ω-3 Fatty Acids and Cardiovascular Diseases: Effects, Mechanisms and Dietary Relevance. *Int J Mol Sci* **2015**, *16*, 22636-22661, doi:10.3390/ijms160922636.
100. Messori, A.; Fadda, V.; Maratea, D.; Trippoli, S. ω-3 Fatty Acid Supplements for Secondary Prevention of Cardiovascular Disease: From "No Proof of Effectiveness" to "Proof of No Effectiveness". *JAMA Internal Medicine* **2013**, *173*, 1466-1468, doi:10.1001/jamainternmed.2013.6638.
101. Curfman, G.; Shehada, E. Icosapent ethyl: scientific and legal controversies. *Open Heart* **2021**, *8*, e001616, doi:10.1136/openhrt-2021-001616.
102. Bhatt, D.L.; Steg, P.G.; Brinton, E.A.; Jacobson, T.A.; Miller, M.; Tardif, J.-C.; Ketchum, S.B.; Doyle Jr, R.T.; Murphy, S.A.; Soni, P.N., et al. Rationale and design of REDUCE-IT: Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial. *Clinical Cardiology* **2017**, *40*, 138-148, doi:https://doi.org/10.1002/clc.22692.
103. Bhatt, D.L.; Steg, P.G.; Miller, M.; Brinton, E.A.; Jacobson, T.A.; Ketchum, S.B.; Doyle, R.T.; Juliano, R.A.; Jiao, L.; Granowitz, C., et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *New England Journal of Medicine* **2019**, *380*, 11-22, doi:10.1056/NEJMoa1812792.
104. Bäck, M.; Hansson, G.K. Omega-3 fatty acids, cardiovascular risk, and the resolution of inflammation. *The FASEB Journal* **2019**, *33*, 1536-1539, doi:10.1096/fj.201802445R.
105. Bhatt, D.L.; Steg, P.G.; Miller, M.; Brinton, E.A.; Jacobson, T.A.; Jiao, L.; Tardif, J.-C.; Gregson, J.; Pocock, S.J.; Ballantyne, C.M. Reduction in First and Total Ischemic Events With Icosapent Ethyl Across Baseline Triglyceride Tertiles. *Journal of the American College of Cardiology* **2019**, *74*, 1159-1161, doi:https://doi.org/10.1016/j.jacc.2019.06.043.
106. Baum, S.J.; Scholz, K.P. Rounding the corner on residual risk: Implications of REDUCE-IT for omega-3 polyunsaturated fatty acids treatment in secondary prevention of atherosclerotic cardiovascular disease. *Clinical Cardiology* **2019**, *42*, 829-838, doi:https://doi.org/10.1002/clc.23220.
107. Ballantyne, C.M.; Bays, H.E.; Kastelein, J.J.; Stein, E.; Isaacsohn, J.L.; Braeckman, R.A.; Soni, P.N. The Effect of Two Doses of AMR101 on Fasting Serum Triglycerides and Other Lipid Parameters in Statin-Treated Patients with Persistent High Triglycerides (≥ 200 and< 500 mg/dL): The ANCHOR Study. *Journal of Clinical Lipidology* **2012**, *6*, 279-280.
108. Bays, H.E.; Ballantyne, C.M.; Kastelein, J.J.; Isaacsohn, J.L.; Braeckman, R.A.; Soni, P.N. Eicosapentaenoic acid ethyl ester (AMR101) therapy in patients with very high triglyceride levels (from the Multi-center, plAcebo-controlled, Randomized, double-blINd, 12-week study with an open-label Extension [MARINE] trial). *The American journal of cardiology* **2011**, *108*, 682-690.
109. Olshansky, B.; Chung, M.K.; Budoff, M.J.; Philip, S.; Jiao, L.; Doyle, J., Ralph T; Copland, C.; Giaquinto, A.; Juliano, R.A.; Bhatt, D.L. Mineral oil: safety and use as placebo in REDUCE-IT and other clinical studies. *European Heart Journal Supplements* **2020**, *22*, J34-J48, doi:10.1093/eurheartj/suaa117.

110. Hu, Y.; Hu, F.B.; Manson, J.E. Marine Omega-3 Supplementation and Cardiovascular Disease: An Updated Meta-Analysis of 13 Randomized Controlled Trials Involving 127 477 Participants. *J Am Heart Assoc* **2019**, *8*, e013543, doi:10.1161/jaha.119.013543.
111. Shen, S.; Gong, C.; Jin, K.; Zhou, L.; Xiao, Y.; Ma, L. Omega-3 Fatty Acid Supplementation and Coronary Heart Disease Risks: A Meta-Analysis of Randomized Controlled Clinical Trials. *Front Nutr* **2022**, *9*, 809311, doi:10.3389/fnut.2022.809311.
112. Yokoyama, M.; Origasa, H.; Matsuzaki, M.; Matsuzawa, Y.; Saito, Y.; Ishikawa, Y.; Oikawa, S.; Sasaki, J.; Hishida, H.; Itakura, H. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet* **2007**, *369*, 1090-1098.
113. Tavazzi, L.; Maggioni, A.P.; Marchioli, R.; Barlera, S.; Franzosi, M.G.; Latini, R.; Lucci, D.; Nicolosi, G.L.; Porcu, M.; Tognoni, G. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet* **2008**, *372*, 1223-1230, doi:10.1016/s0140-6736(08)61239-8.
114. Manson, J.E.; Cook, N.R.; Lee, I.-M.; Christen, W.; Bassuk, S.S.; Mora, S.; Gibson, H.; Gordon, D.; Copeland, T.; D'Agostino, D., et al. Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease. *New England Journal of Medicine* **2019**, *380*, 33-44, doi:10.1056/NEJMoa1809944.
115. The Origin Trial Investigators. n–3 Fatty Acids and Cardiovascular Outcomes in Patients with Dysglycemia. *New England Journal of Medicine* **2012**, *367*, 309-318, doi:10.1056/NEJMoa1203859.
116. The ASCEND Study Collaborative Group. Effects of n−3 fatty acid supplements in diabetes mellitus. *New England Journal of Medicine* **2018**, *0*, null, doi:10.1056/NEJMoa1804989.
117. Budoff, M.J.; Bhatt, D.L.; Kinninger, A.; Lakshmanan, S.; Muhlestein, J.B.; Le, V.T.; May, H.T.; Shaikh, K.; Shekar, C.; Roy, S.K., et al. Effect of icosapent ethyl on progression of coronary atherosclerosis in patients with elevated triglycerides on statin therapy: final results of the EVAPORATE trial. *European Heart Journal* **2020**, *41*, 3925-3932, doi:10.1093/eurheartj/ehaa652.
118. Watanabe, T.; Ando, K.; Daidoji, H.; Otaki, Y.; Sugawara, S.; Matsui, M.; Ikeno, E.; Hirono, O.; Miyawaki, H.; Yashiro, Y., et al. A randomized controlled trial of eicosapentaenoic acid in patients with coronary heart disease on statins. *J Cardiol* **2017**, *70*, 537-544, doi:10.1016/j.jjcc.2017.07.007.
119. Nicholls, S.J.; Lincoff, A.M.; Garcia, M.; Bash, D.; Ballantyne, C.M.; Barter, P.J.; Davidson, M.H.; Kastelein, J.J.P.; Koenig, W.; McGuire, D.K., et al. Effect of High-Dose Omega-3 Fatty Acids vs Corn Oil on Major Adverse Cardiovascular Events in Patients at High Cardiovascular Risk: The STRENGTH Randomized Clinical Trial. *JAMA* **2020**, *324*, 2268-2280, doi:10.1001/jama.2020.22258.
120. Kalstad, A.A.; Myhre, P.L.; Laake, K.; Tveit, S.H.; Schmidt, E.B.; Smith, P.; Nilsen, D.W.T.; Tveit, A.; Fagerland, M.W.; Solheim, S., et al. Effects of n-3 Fatty Acid Supplements in Elderly Patients After Myocardial Infarction. *Circulation* **2021**, *143*, 528-539, doi:doi:10.1161/CIRCULATIONAHA.120.052209.
121. Kataoka, Y.; Uno, K.; Puri, R.; Nicholls, S.J. Epanova® and hypertriglyceridemia: pharmacological mechanisms and clinical efficacy. *Future Cardiology* **2013**, *9*, 177-186, doi:10.2217/fca.13.4.
122. Nicholls, S.J.; Lincoff, A.M.; Bash, D.; Ballantyne, C.M.; Barter, P.J.; Davidson, M.H.; Kastelein, J.J.P.; Koenig, W.; McGuire, D.K.; Mozaffarian, D., et al. Assessment of omega-3 carboxylic acids in statin-treated patients with high levels of triglycerides and low levels of high-density lipoprotein cholesterol: Rationale and design of the STRENGTH trial. *Clinical Cardiology* **2018**, *41*, 1281-1288, doi:https://doi.org/10.1002/clc.23055.
123. Casula, M.; Soranna, D.; Catapano, A.L.; Corrao, G. Long-term effect of high dose omega-3 fatty acid supplementation for secondary prevention of cardiovascular outcomes: A meta-analysis of randomized, double blind, placebo controlled trials. *Atherosclerosis Supplements* **2013**, *14*, 243-251, doi:http://dx.doi.org/10.1016/S1567-5688(13)70005-9.
124. Goff, Z.D.; Nissen, S.E. N-3 polyunsaturated fatty acids for cardiovascular risk. *Curr Opin Cardiol* **2022**, *37*, 356-363, doi:10.1097/hco.0000000000000962.
125. Nissen, S.E.; Lincoff, A.M.; Wolski, K.; Ballantyne, C.M.; Kastelein, J.J.P.; Ridker, P.M.; Ray, K.K.; McGuire, D.K.; Mozaffarian, D.; Koenig, W., et al. Association Between Achieved ω-3 Fatty Acid Levels and Major Adverse Cardiovascular Outcomes in Patients With High Cardiovascular Risk: A Secondary Analysis of the STRENGTH Trial. *JAMA Cardiology* **2021**, *6*, 910-917, doi:10.1001/jamacardio.2021.1157.
126. Doi, T.; Langsted, A.; Nordestgaard, B.G. A possible explanation for the contrasting results of REDUCE-IT vs. STRENGTH: cohort study mimicking trial designs. *European Heart Journal* **2021**, *42*, 4807-4817, doi:10.1093/eurheartj/ehab555.

127. Ahmmed, M.K.; Ahmmed, F.; Tian, H.; Carne, A.; Bekhit, A.E.-D. Marine omega-3 (n-3) phospholipids: A comprehensive review of their properties, sources, bioavailability, and relation to brain health. *Comprehensive Reviews in Food Science and Food Safety* **2020**, *19*, 64-123, doi:10.1111/1541-4337.12510.
128. Konagai, C.; Yanagimoto, K.; Hayamizu, K.; Han, L.; Tsuji, T.; Koga, Y. Effects of krill oil containing n-3 polyunsaturated fatty acids in phospholipid form on human brain function: a randomized controlled trial in healthy elderly volunteers. *Clinical Interventions in Aging* **2013**, *8*, 1247-1257, doi:10.2147/CIA.S50349.
129. Schuchardt, J.P.; Hahn, A. Bioavailability of long-chain omega-3 fatty acids. *Prostaglandins Other Lipid Mediat.* **2013**, *89*, 1-8, doi:https://doi.org/10.1016/j.plefa.2013.03.010.
130. Köhler, A.; Sarkkinen, E.; Tapola, N.; Niskanen, T.; Bruheim, I. Bioavailability of fatty acids from krill oil, krill meal and fish oil in healthy subjects--a randomized, single-dose, cross-over trial. *Lipids Health Dis* **2015**, *14*, 19, doi:10.1186/s12944-015-0015-4.
131. Schuchardt, J.P.; Schneider, I.; Meyer, H.; Neubronner, J.; von Schacky, C.; Hahn, A. Incorporation of EPA and DHA into plasma phospholipids in response to different omega-3 fatty acid formulations - a comparative bioavailability study of fish oil vs. krill oil. *Lipids in Health and Disease* **2011**, *10*, 145, doi:10.1186/1476-511x-10-145.
132. Lapointe, J.-F.; Harvey, L.; Aziz, S.; Jordan, H.; Hegele, R.A.; Lemieux, P. A single-dose, comparative bioavailability study of a formulation containing OM3 as phospholipid and free fatty acid to an ethyl ester formulation in the fasting and fed states. *Clinical Therapeutics* **2019**, *41*, 426-444, doi:https://doi.org/10.1016/j.clinthera.2019.01.017.
133. Akram, W.; Rihan, M.; Ahmed, S.; Arora, S.; Ahmad, S.; Vashishth, R. Marine-Derived Compounds Applied in Cardiovascular Diseases: Submerged Medicinal Industry. *Marine Drugs* **2023**, *21*, 193.
134. Nomikos, T.; Karantonis, H.C.; Skarvelis, C.; Demopoulos, C.A.; Zabetakis, I. Antiatherogenic properties of lipid fractions of raw and fried fish. *Food Chemistry* **2006**, *96*, 29-35.
135. Tsoupras, A.; O'Keeffe, E.; Lordan, R.; Redfern, S.; Zabetakis, I. Bioprospecting for antithrombotic polar lipids from salmon, herring, and boarfish by-products. *Foods* **2019**, *8*, 416, doi:https://doi.org/10.3390/foods8090416.
136. Tsoupras, A.; Lordan, R.; Demuru, M.; Shiels, K.; Saha, S.K.; Nasopoulou, C.; Zabetakis, I. Structural elucidation of Irish organic farmed salmon (*Salmo salar*) polar lipids with antithrombotic activities. *Marine Drugs* **2018**, *16*, 176, doi:https://doi.org/10.3390/md16060176.
137. Tsoupras, A.; Lordan, R.; Shiels, K.; Saha, S.K.; Nasopoulou, C.; Zabetakis, I. In vitro antithrombotic properties of salmon (*Salmo salar*) phospholipids in a novel food-grade extract. *Marine Drugs* **2019**, *17*, 62, doi:https://doi.org/10.3390/md17010062.
138. Fountoulaki, E.; Vasilaki, A.; Hurtado, R.; Grigorakis, K.; Karacostas, I.; Nengas, I.; Rigos, G.; Kotzamanis, Y.; Venou, B.; Alexis, M.N. Fish oil substitution by vegetable oils in commercial diets for gilthead sea bream (Sparus aurata L.); effects on growth performance, flesh quality and fillet fatty acid profile: Recovery of fatty acid profiles by a fish oil finishing diet under fluctuating water temperatures. *Aquaculture* **2009**, *289*, 317-326, doi:https://doi.org/10.1016/j.aquaculture.2009.01.023.
139. Bell, J.G.; Tocher, D.R.; Henderson, R.J.; Dick, J.R.; Crampton, V.O. Altered fatty acid compositions in atlantic salmon (Salmo salar) fed diets containing linseed and rapeseed oils can be partially restored by a subsequent fish oil finishing diet. *J Nutr* **2003**, *133*, 2793-2801, doi:10.1093/jn/133.9.2793.
140. Montero, D.; Robaina, L.; Caballero, M.J.; Ginés, R.; Izquierdo, M.S. Growth, feed utilization and flesh quality of European sea bass (Dicentrarchus labrax) fed diets containing vegetable oils: A time-course study on the effect of a re-feeding period with a 100% fish oil diet. *Aquaculture* **2005**, *248*, 121-134, doi:https://doi.org/10.1016/j.aquaculture.2005.03.003.
141. Tsantila, N.; Karantonis, H.C.; Perrea, D.N.; Theocharis, S.E.; Iliopoulos, D.G.; Antonopoulou, S.; Demopoulos, C.A. Antithrombotic and antiatherosclerotic properties of olive oil and olive pomace polar extracts in rabbits. *Mediators of Inflammation* **2007**, *2007*.
142. Karantonis, H.C.; Tsantila, N.; Stamatakis, G.; Samiotaki, M.; Panayotou, G.; Antonopoulou, S.; Demopoulos, C.A. Bioactive polar lipids in olive oil, pomace and waste byproducts. *J Food Biochem* **2008**, *32*, 443-459, doi:10.1111/j.1745-4514.2008.00160.x.
143. Nasopoulou, C.; Karantonis, H.C.; Perrea, D.N.; Theocharis, S.E.; Iliopoulos, D.G.; Demopoulos, C.A.; Zabetakis, I. In vivo anti-atherogenic properties of cultured gilthead sea bream (*Sparus aurata*) polar lipid extracts in hypercholesterolaemic rabbits. *Food Chemistry* **2010**, *120*, 831-836, doi:http://dx.doi.org/10.1016/j.foodchem.2009.11.023.

144. Nasopoulou, C.; Smith, T.; Detopoulou, M.; Tsikrika, C.; Papaharisis, L.; Barkas, D.; Zabetakis, I. Structural elucidation of olive pomace fed sea bass (*Dicentrarchus labrax*) polar lipids with cardioprotective activities. *Food Chemistry* **2014**, *145*, 1097-1105, doi:http://dx.doi.org/10.1016/j.foodchem.2013.08.091.
145. Nasopoulou, C.; Tsoupras, A.B.; Karantonis, H.C.; Demopoulos, C.A.; Zabetakis, I. Fish polar lipids retard atherosclerosis in rabbits by down-regulating PAF biosynthesis and up-regulating PAF catabolism. *Lipids in Health and Disease* **2011**, *10*, 1-18, doi:doi:10.1186/1476-511X-10-213.
146. Tsoupras, A.B.; Fragopoulou, E.; Iatrou, C.; Demopoulos, C.A. In vitro protective effects of olive pomace polar lipids towards platelet activating factor metabolism in human renal cells. *Curr Top Nutraceutical Res* **2011**, *9*, 105.
147. Petsini, F.; Ntzouvani, A.; Detopoulou, M.; Papakonstantinou, V.D.; Kalogeropoulos, N.; Fragopoulou, E.; Nomikos, T.; Kontogianni, M.D.; Antonopoulou, S. Consumption of Farmed Fish, Fed with an Olive-Pomace Enriched Diet, and Its Effect on the Inflammatory, Redox, and Platelet-Activating Factor Enzyme Profile of Apparently Healthy Adults: A Double-Blind Randomized Crossover Trial. *Foods* **2022**, *11*, 2105.
148. Sioriki, E.; Smith, T.K.; Demopoulos, C.A.; Zabetakis, I. Structure and cardioprotective activities of polar lipids of olive pomace, olive pomace-enriched fish feed and olive pomace fed gilthead sea bream (*Sparus aurata*). *Food Res. Int.* **2016**, *83*, 143-151, doi:http://dx.doi.org/10.1016/j.foodres.2016.03.015.
149. Morphis, G.; Kyriazopoulou, A.; Nasopoulou, C.; Sioriki, E.; Demopoulos, C.A.; Zabetakis, I. Assessment of the in Vitro antithrombotic properties of sardine (Sardina pilchardus) fillet lipids and cod liver oil. *Fishes* **2016**, *1*, 1-15.
150. Nasopoulou, C.; Gogaki, V.; Stamatakis, G.; Papaharisis, L.; Demopoulos, C.; Zabetakis, I. Evaluation of the in Vitro Anti-Atherogenic Properties of Lipid Fractions of Olive Pomace, Olive Pomace Enriched Fish Feed and Gilthead Sea Bream (Sparus aurata) Fed with Olive Pomace Enriched Fish Feed. *Marine Drugs* **2013**, *11*, 3676.
151. Xie, D.; Li, P.; Zhu, Y.; He, J.; Zhang, M.; Liu, K.; Lin, H.; Zhai, H.; Li, X.; Ma, Y. Comparative bioactivity profile of phospholipids from three marine byproducts based on the zebrafish model. *Journal of Food Biochemistry* **2022**, *46*, e14229, doi:https://doi.org/10.1111/jfbc.14229.
152. Lordan, R.; Walsh, A.M.; Crispie, F.; Finnegan, L.; Cotter, P.D.; Zabetakis, I. The effect of ovine milk fermentation on the antithrombotic properties of polar lipids. *J. Funct. Foods* **2019**, *54*, 289-300, doi:https://doi.org/10.1016/j.jff.2019.01.029.
153. Poutzalis, S.; Lordan, R.; Nasopoulou, C.; Zabetakis, I. Phospholipids of goat and sheep origin: Structural and functional studies. *Small Ruminant Res.* **2018**, *167*, 39-47., doi:https://doi.org/10.1016/j.smallrumres.2018.07.015.
154. Antonopoulou, S.; Semidalas, C.E.; Koussissis, S.; Demopoulos, C.A. Platelet-activating factor (PAF) antagonists in foods: a study of lipids with PAF or anti-PAF-like activity in cow's milk and yogurt. *Journal of Agriculture and Food Chemistry* **1996**, *44*, 3047-3051, doi:https://doi.org/10.1021/jf950619y.
155. Falk-Petersen, S.; Sargent, J.R.; Henderson, J.; Hegseth, E.N.; Hop, H.; Okolodkov, Y.B. Lipids and fatty acids in ice algae and phytoplankton from the Marginal Ice Zone in the Barents Sea. *Polar Biology* **1998**, *20*, 41-47, doi:10.1007/s003000050274.
156. Moreira, A.S.P.; Gonçalves, J.; Conde, T.A.; Couto, D.; Melo, T.; Maia, I.B.; Pereira, H.; Silva, J.; Domingues, M.R.; Nunes, C. Chrysotila pseudoroscoffensis as a source of high-value polar lipids with antioxidant activity: A lipidomic approach. *Algal Research* **2022**, *66*, 102756, doi:https://doi.org/10.1016/j.algal.2022.102756.
157. Robertson, R.; Guihéneuf, F.; Bahar, B.; Schmid, M.; Stengel, D.; Fitzgerald, G.; Ross, R.; Stanton, C. The Anti-Inflammatory Effect of Algae-Derived Lipid Extracts on Lipopolysaccharide (LPS)-Stimulated Human THP-1 Macrophages. *Marine Drugs* **2015**, *13*, 5402, doi:https://doi.org/10.3390/md13085402.
158. Jesionowska, M.; Ovadia, J.; Hockemeyer, K.; Clews, A.C.; Xu, Y. EPA and DHA in microalgae: Health benefits, biosynthesis, and metabolic engineering advances. *Journal of the American Oil Chemists' Society n/a*, doi:https://doi.org/10.1002/aocs.12718.
159. da Costa, E.; Amaro, H.M.; Melo, T.; Guedes, A.C.; Domingues, M.R. Screening for polar lipids, antioxidant, and anti-inflammatory activities of Gloeothece sp. lipid extracts pursuing new phytochemicals from cyanobacteria. *Journal of Applied Phycology* **2020**, *32*, 3015-3030, doi:10.1007/s10811-020-02173-6.
160. Novik, G.I.; Astapovich, N.I.; Pasciak, M.; Gamian, A. [Biological activity of polar lipids from bifidobacteria]. *Mikrobiologiia* **2005**, *74*, 781-787.

161. Shiels, K.; Tsoupras, A.; Lordan, R.; Zabetakis, I.; Murray, P.; Kumar Saha, S. Anti-inflammatory and antithrombotic properties of polar lipid extracts, rich in unsaturated fatty acids, from the Irish marine cyanobacterium Spirulina subsalsa. *Journal of Functional Foods* **2022**, *94*, 105124, doi:https://doi.org/10.1016/j.jff.2022.105124.
162. Shiels, K.; Tsoupras, A.; Lordan, R.; Nasopoulou, C.; Zabetakis, I.; Murray, P.; Saha, S.K. Bioactive Lipids of Marine Microalga Chlorococcum sp. SABC 012504 with Anti-Inflammatory and Anti-Thrombotic Activities. *Marine Drugs* **2021**, *19*, 28.
163. Lopes, D.; Melo, T.; Meneses, J.; Abreu, M.H.; Pereira, R.; Domingues, P.; Lillebø, A.I.; Calado, R.; Domingues, M.R. A New Look for the Red Macroalga Palmaria palmata: A Seafood with Polar Lipids Rich in EPA and with Antioxidant Properties. *Mar Drugs* **2019**, *17*, doi:10.3390/md17090533.
164. da Costa, E.; Melo, T.; Reis, M.; Domingues, P.; Calado, R.; Abreu, M.H.; Domingues, M.R. Polar Lipids Composition, Antioxidant and Anti-Inflammatory Activities of the Atlantic Red Seaweed Grateloupia turuturu. *Mar Drugs* **2021**, *19*, doi:10.3390/md19080414.