Health effects of omega-3 polyunsaturated fatty acids in common diseases

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Abstract

Omega-3 polyunsaturated fatty acids (n-3 PUFAs), such as alpha-linolenic, eicosapentaenoic, and docosahexaenoic acids mostly exist in marine-derived foods, and have shown beneficial effects for hypertriglyceridemia, endothelial function, inflammation, and oxidative stress. Studies suggest that n-3 PUFAs can regulate the activity of NF-κB, Nrf2, SREBP-1c, and PPARα, which are linked to inflammations, ROS homeostasis, and lipid metabolism. Several epidemiological trials and physiological studies indicated protective effect of n-3 PUFAs against various common diseases such as cardiovascular diseases, diabetes mellitus, and non-alcoholic fatty liver disease. This review summarises the findings of many such studies highlighting the beneficial effects of n-3 PUFAs.

Keywords

n-3 PUFAs, beneficial effect, disease risk factors, common diseases

Introduction

Polyunsaturated fatty acids (PUFAs) carry several double bonds. As the name suggests, the first double-bond in omega-3 polyunsaturated fatty acids (n-3 PUFAs) is at the third carbon from the methyl end. Alpha-linolenic (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) are the three major n-3 PUFAs (Calder, 2012). ALA is mainly produced in plants such as flaxseed, canola, and butternut, while EPA and DHA are mostly produced in marine animals such as fish, algae, and seals. Humans cannot endogenously synthesise n-3 PUFAs, and therefore mainly depend on diet sources. In humans, ALA can be biochemically converted into EPA and DHA; however, the conversion rate is very poor (ALA to EPA: 0.2 - 8%; ALA to DHA: 0 - 4%) (Mozaffarian and Wu, 2011). Due to this, marine food has emerged as an important direct source of EPA and DHA. Additionally, the fish oil in the form of ethyl esters (EEs) or acylglycerols is a popular commercially available n-3 PUFA supplement. Likewise, other marine-sourced oils, such as algal, fungal, and krill oils have been commercially accepted for their rich n-3 PUFA content (Shahidi and Ambigaipalan, 2018).

Various in vitro, animal, and clinical studies have shown antioxidant, anti-inflammatory, and cardiovascular-regulatory functions of n-3 PUFAs (Mozaffarian and Wu, 2011). Accordingly, n-3 PUFAs are conceived as healthy fats. In 2007, the American Dietetic Association (ADA) and Dietitians of Canada (DC) declared that the basal n-3 PUFA requirement of 500 mg/day in adults is equivalent to 8 oz. of fish per week (Kris-Etherton et al., 2007). In 2013, the DC again emphasised at least twice per week consumption of fish diet approximately provides 0.3 - 0.45 g n-3 PUFAs each day (Shahidi and Ambigaipalan, 2018).

Given the numerous physiological functions of n-3 PUFAs, they have been extensively studied for their protective effect against various diseases (Innes and Calder, 2020). This review thus aims to briefly summarise the beneficial effects of n-3 PUFAs with potential underlying mechanisms in several diseases.

n-3 PUFAs alleviate potential disease risk

Dietary triglycerides (TGs) enter the blood circulation from the small intestine as chylomicrons, and get hydrolysed by lipoprotein lipase (LPL) into free fatty acids (FFA), which are then consumed as the energy source by various cells such as muscle cells, while the excess TG is stored in the liver. In case of increased energy demand, hepatic TG combined with apolipoprotein B-100, also known as very-low-density lipoprotein (VLDL), is secreted back into the blood, where LPL can transform it into LDL for muscle cells (Alves-Bezerra and Cohen, 2017). High TG level, mostly a result of unhealthy lifestyle and diet, can cause endothelial dysfunction, which leads to decreased flow-mediated dilatation of blood vessels which could progress to other disorders (Reiner, 2017). Therefore, a high TG level is
Hyperlipidaemia

Hyperlipidaemia (TG level ≥ 1.7 mmol/L or ≥ 150 mg/dL) is often associated with secondary disorders such as cardiovascular disease (CD) and/or type 2 diabetes mellitus (T2DM). Approximately 25% of the US adult population is hyperlipidemic, while severe hyperlipidaemia (≥ 5.6 mmol/L or ≥ 500 mg/dL) is a well-established initiation factor for secondary diseases (Toth, 2016). Several studies showed that n-3 PUFAs can lower the TG level in hyperlipidemic individuals. Zeman et al. (2006) showed that hyperlipidemic individuals who received n-3 PUFAs for three months showed a significant decrease in the plasma TG level than the individuals of the control group. Similarly, Zhu et al. (2008) showed a remarkable decrease of plasma TG level among hyperlipidemic participants after 24-week administration of n-3 PUFAs. Chan et al. (2016) also showed similar results. Besides, a study of 176 hyperlipidemic subjects, which were randomly assigned into the placebo-controlled, 1, 2, and 3 g n-3 PUFAs treatment groups, showed a dose-dependent decrease in plasma TG level in a 2-month follow-up study (Oh et al., 2014).

n-3 PUFAs can lower the plasma TG level via three major pathways: (1) n-3 PUFA supplementation inhibits the activity of sterol receptor element-binding protein-1c (SREBP-1c), which is an activator of two hepatic TG synthesis enzymes, namely the diacylglycerol acetyl-transferase (DGAT) and phosphatidic acid phosphohydrolase (PA). Lowering SREBP-1c activity reduces TG production, and secretion of VLDL (Nakamura et al., 2004; Harris and Bulchandani, 2006); (2) n-3 PUFAs can upregulate β-oxidation of the fatty acid substrates of hepatic TG synthesis (Pirillo and Catapano, 2015) via interaction with peroxisome proliferator-activated receptor-α (PPARα), which is a key regulatory transcription factor for β-oxidation of fatty acids in mitochondria and peroxisome (Nakamura et al., 2004), eventually, the lack of essential substrates suppresses the hepatic TG synthesis (Shearer et al., 2012); and (3) n-3 PUFAs accelerate hepatic TG clearance by inducing lipolysis via insulin-promoted lipoprotein lipase (LPL) (Park and Harris, 2003). Though the pathways involved in n-3 PUFAs-mediated lowering of TG are well-known, the mechanism of n-3 PUFA’s interaction with the related enzymes is not clear (Table 1).

Inflammatory response

A study showed that the levels of inflammatory cytokines, including IL-6, IL-10, and TNF-α are positively related to TG level (Gonzalez et al., 2018). Since n-3 PUFAs can reduce TG level, an association between n-3 PUFAs and inflammatory response was explored. De Caterina and Libby (1996) showed that n-3 PUFAs supplementation significantly reduced the IL-1α-induced levels of IL-6 and IL-8 in human vein endothelial cells, thus suppressing inflammatory response from IL-1α. Another study showed that n-3 PUFA pre-treatment dramatically reduced the LPS-induced level of IL-10 in RAW 264.7 cells (Babcock et al., 2002). Recently, a study suggested that n-3 PUFAs can remarkably

<table>
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<th>Pathway</th>
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<td>Inhibiting the enzymes of TG synthesis by downregulating the activity of SREBP-1c</td>
<td>Suppressing TG synthesis</td>
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<tr>
<td>Enhancing β-oxidation of fatty acids by upregulating the activity of PPARα</td>
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<td>Promoting the action of LPL</td>
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Table 1. The TG-lowering mechanisms of n-3 PUFAs.
downregulate the gene expression of inflammatory cytokines IL-1β and TNF-α in THP-1 macrophages (Allam-Ndoul et al., 2016). Similarly, a rat study showed that high-fat diet-induced levels of TNF-α and IL-1β were significantly alleviated after treatment with n-3 PUFAs (Breetha and Ramaprasad, 2018). In the apical periodontitis (AP) rat model too, n-3 PUFAs treatment led to a decrease of inflammatory cytokines TNF-α, IL-6, IL-1β, and IL-17 (Azuma et al., 2018). Moreover, a clinical trial on 324 obese subjects aged 20 to 40 indicated that n-3 PUFA supplementation for 8-week alleviated inflammatory response by downregulating CRP and IL-6 (Ramel et al., 2010).

The inflammatory response involves the activation of various transcription factors, including NF-κB, which plays an important role in many inflammatory signalling pathways. NF-κB regulates some inflammatory cytokines (IL-1, IL-2, IL-6, IL-12, TNF-α, and etc.), chemokines (IL-8, MIP-1α, MCP1, and etc.), adhesion molecules (ICAM, VCAM, E-selectin, and etc.), and inducible effector enzymes (iNOS and COX-2) (Ghosh and Karin, 2002). In the inactivated state, NF-κB dimer remains bound to inhibitor protein IκB in the cytoplasm; however, when cell is exposed to stress condition, the inhibitor IκB is phosphorylated, thus releasing NF-κB. The activated NF-κB protein is then translocated into the nucleus to promote the expression of inflammatory proteins (Perkins, 2007).

Lo et al. (1999) showed that n-3 PUFA supplementation significantly inhibited the LPS-induced expression of TNF-α and NF-κB in RAW 264.7 cells. Novak et al. (2003) showed that n-3 PUFAs promoted the inactivation of NF-κB by reducing the phosphorylation of IκB, which in turn reduced the LPS-induced level of TNF-α in RAW 264.7 cells. In LPS-exposed human monocytic THP-1 cells too, n-3 PUFAs treatment inhibited the nuclear translocation of NF-κB by suppressing the degradation of IκB, which, in turn, reduced the LPS-induced level of TNF-α (Zhao et al., 2004). Similar observations were also made in animal models. Hudert et al. (2006) suggested that enhanced levels of n-3 PUFAs downregulated the activity of NF-κB, thus reducing the generation of TNF-α and IL-1β in the mice colitis model. Another study in the rat colitis model showed that n-3 PUFAs may alleviate inflammatory response via inhibition of NF-κB which suppresses the activity of inflammatory cells (Triantafyllidis et al., 2015). In the hepatic ischemia/reperfusion (I/R)-injury rat model, the hyperactivated NF-κB and increased level of TNF-α and IL-1β were both reversed by n-3 PUFAs via enhanced stability of IκB (Zuniga et al., 2011). In the testicular I/R-injury rat model too, n-3 PUFAs could attenuate inflammatory response by regulating the activity of NF-κB (Qi et al., 2017). A human clinical trial, involving the patients with sickle cell disease (SCD), showed that 1-year intervention with n-3 PUFAs downregulated the level of inflammatory cytokines and NF-κB in the patients as compared to the control group (Daak et al., 2015). Overall, these findings illustrate that n-3 PUFA-mediated regulation of inflammatory response depends on the IκB-mediated inhibition of NF-κB.

Oxidative stress

Intracellular metabolism generates reactive oxygen species (ROS) including superoxide, hydroxyl radical, and singlet oxygen which are highly unstable and reactive molecules, and can impair the cellular components such as proteins, lipids, and nucleic acids. Therefore, intracellular antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT) eliminate ROS and function as preventative measures. An imbalance of ROS production and antioxidant enzymes, named oxidative stress, can damage cellular function, thus causing cell death (Zhang et al., 2016). Intracellular ROS can be upregulated by inflammatory cytokines such as TNF-α and IL-1β (Clauzure et al., 2014; Roberge et al., 2014). Also, ROS can trigger the activation of NF-κB by inducing phosphorylation and/or degradation of IκB (Zhang et al., 2016). Upregulated inflammatory cytokines promote oxidative stress, which further aggravates the inflammatory reaction via the NF-κB pathway.

n-3 PUFA supplementation can reduce the level of ROS inducing inflammatory cytokines, thus showing a kind of antioxidant effect. Che et al. (2018) showed that n-3 PUFAs significantly enhanced the level of SOD to protect rat pheochromocytoma (P12) cells from oxidative damage. Under oxidative stress, cardiomyocytes (H9c2) cells showed an increased level of MDA (an end-product of oxidative damage), while the levels of antioxidant enzymes SOD, GPx, and CAT decreased. n-3 PUFA treatment also effectively ameliorated the negative effect of oxidative stress in H9c2 cells (Varghese et al., 2017). In ESC-derived cardiac lineage cells, pre-treatment with n-3 PUFAs dramatically inhibited the H2O2-induced oxidative stress (Shabani et al., 2019). The antioxidant effect of n-3 PUFAs has also been verified in a human clinical trial. Mas et al. (2010) showed that overweight participants who received n-3 PUFAs 4 gm/day for
six weeks exhibited a remarkable decrease in plasma F2-isoprostane (a marker of oxidative damage) level, as compared to those who received olive oil. A randomised controlled trial of 105 overweight subjects showed that as compared to the control group, the n-3 PUFA treatment group had a lower level of F2-isoprostane during the 4-month follow-up period (Kiecolt-Glaser et al., 2013). Recently, another study in type 2 diabetic patients suggested that MDA and F2-isoprostane levels were remarkably reduced after administration with n-3 PUFAs for two weeks (Vericel et al., 2015).

Although the above studies demonstrated that n-3 PUFAs can attenuate oxidative stress-induced damage, the mechanism remains unclear. Since mitochondria and NADPH oxidases are the main sources of ROS, mitochondrial dysfunction is considered the main causative factor of oxidative stress. Emerging evidence indicates that inflammatory response is a result of mitochondrial abnormality which aggravates intracellular ROS levels (Dan Dunn et al., 2015; Angelova and Abramov, 2018). A study showed that n-3 PUFAs can effectively ameliorate oxidative damage and mitochondrial dysfunction both in vivo and in vitro (Zhang et al., 2018a). n-3 PUFAs could improve oxidative damage by inhibiting the activity of mitochondrial respiratory chain enzymes in rats’ brain tissue under oxidative stress (Carvalho-Silva et al., 2019). Nuclear factor E2-related factor 2 (Nrf2) is a transcription factor that regulates the expression of various antioxidant enzymes including haem oxygenase 1 (HO-1). Under normal conditions, Nrf2 is silenced by Keap1 (Kelch-like ECH-associated protein 1), but under oxidative stress, it gets released from Keap1 for nuclear translocation, where it upregulates the transcription of antioxidant enzymes (Tonelli et al., 2018). Zhang et al. (2014) suggested that protective effects of n-3 PUFAs were in part due to the activation of Nrf2 in the brain injury mouse model. In another study, hepatic injury or a high-fat diet significantly downregulated Nrf2/HO-1 in mice, whereas n-3 PUFA treatment dramatically alleviated hepatic injury by enhancing the Nrf2/OH-1 activity (Gonzalez et al., 2018). Similarly, Yang et al. (2013) showed that n-3 PUFAs enhanced nuclear translocation of Nrf2, thus promoting the latter’s activity. All these findings suggest that n-3 PUFAs show antioxidant effect via two major pathways: (1) by reducing ROS production from mitochondrial dysfunction, and (2) by eliminating the redundant ROS by Nrf2 activation (Figure 1).

Protective effect of n-3 PUFAs

Several common diseases of the modern world have emerged as serious health issues. In 2016, about 121.5 million young adults (≥ 20 years) had more than one type of cardiovascular disease (CVD), and approximately 17.6 million deaths were attributed to CVD worldwide. DM is another prevalent disease. From 2013 to 2016, about 9.8% of US adults (≈ 26 million) were diagnosed with DM, costing ~327 billion dollars to patients in 2017 (Benjamin et al., 2019). Similarly, non-alcoholic fatty liver disease (NAFLD) is also on a rising trajectory affecting around 25.24% of the global population in 2016 (Younossi et al., 2016). High TG level, inflammation, and oxidative stress are general clinical characteristics of these disorders. High TG level is positively linked to endothelial dysfunction,

![Figure 1](image-url)

Figure 1. An unhealthy diet and lifestyle-induced high TG level can promote a series of intracellular negative reactions, while n-3 PUFA supplementation effectively reduces the enhanced TG level, and alleviates oxidative damage by promoting Nrf2 activation.
an important contributor to cardiovascular events, which is further aggravated by inflammation and oxidative stress (Steven et al., 2019). Similarly, high TG level can trigger DM by impairing insulin synthesis due to TG deposition-induced abnormality of insulin β-cells (Raz et al., 2005). Kozakova et al. (2019) found that as compared to healthy individuals, type 2 diabetes (T2D) patients exhibited higher plasm levels of IL-6 and IL-8. Notably, NAFLD is also regarded as a consequence of excessive TG deposition in the liver, which can further deteriorate to non-alcoholic steatohepatitis (NASH). After a series of inflammatory events and oxidative damages, NASH can finally develop into hepatic fibrosis (Peverill et al., 2014). Overall, these findings highlight that common lifestyle diseases are aggravated by TG levels, which can be countered with n-3 PUFA supplementation.

Cardiovascular disease (CVD)

In the 1970s, some Danish physicians found that the risk of coronary heart disease (CHD) among Greenland Eskimos was significantly lower than those who lived in Denmark. They observed that n-3 PUFA-rich fish diet led to a higher concentration of n-3 PUFAs in Eskimos blood (Bang et al., 1976). Subsequently, more epidemiological studies were performed to validate this claim. In 1985, Kromhout et al. (1985) showed that CHD-related mortality was about 50% lower in those who eat fish at least 30 g/day than those who rarely consumed fish. This was also supported by the American nurses’ health study which started in 1976 with a 16-year follow-up and included 84,688 healthy women nurses, aged 30 to 55. The study showed an inverse association between CHD risk and fish consumption (Hu et al., 2002). Another 3-year follow-up study among 18,244 healthy men (aged 45 to 64) in Shanghai, China suggested a significant link between fish diet and lower risk of fatal myocardial infarction (MI) (Yuan et al., 2001). The same was reported in Japan Public Health Centre-based (JPHC) study, which supervised 41,578 Japanese middle-aged individuals between 1990 and 2001. The study found a lower CVD risk among more fish-consuming individuals than those who had less fish (Iso et al., 2006).

Apart from the above-discussed studies, several clinical trials also established the protective effect of n-3 PUFAs. In 2018, an RCT (randomised controlled trial) of 421,309 participants who were free of CVD risk showed a 10% decline of CVD mortality in those who consumed more fish than those who consumed less (Zhang et al., 2018b). Another RCT of 427,678 healthy UK individuals in 2020 indicated a dramatic correlation between higher n-3 PUFAs intake and lower CVD events, including CVD-related mortality (Li et al., 2020).

Additionally, the beneficial effect of n-3 PUFAs as secondary prevention measure was also investigated. A GISSI-Prevenzione trial of 11,323 MI survivors for a 3.5-year follow-up study showed that n-3 PUFA treatment reduced CVD mortality by about 30% as compared to the placebo (Marchioli et al., 2002). A JELIS trial with a 5-year follow-up of patients with a history of CVD showed that statin supplemented with EPA reduced CVD events by 19% than statin alone (Yokoyama et al., 2007). Most recently in 2019, a 4.9-year follow-up RCT of 8,179 hypertriglyceridemia patients suggested that CVD events among patients treated with EPA supplementation were remarkably lower (71% in secondary prevention trial) than those in the placebo group (Bhatt et al., 2019).

Meta-analyses of RCTs showed a significant preventive effect of n-3 PUFAs. A meta-analysis of 11 RCTs, including 39,044 patients with a history of CVD, found that the patients who took 1.8 gm/day EPA/DHA exhibited a significantly lower CVD risk than those in the control group (Marik and Varon, 2009). In 2013, a meta-analysis of 11 RCTs investigated the effect of n-3 PUFA supplementation (1 gm/day for at least one year), and found that as compared to those who took a placebo, 32% reduction of cardiac death, 33% reduction of sudden death, and 25% reduction of MI was noticed in those who received n-3 PUFAs (Casula et al., 2013). Another meta-analysis of 14 RCTs in 2014, including 32,656 individuals with CHD, showed a 7% reduction in CVD events, 12% reduction in death from cardiac causes, 14% reduction in sudden cardiac death, and 8% reduction in all-cause mortality among patients who received n-3 PUFAs as compared to the control group (Wen et al., 2014).

Recently, a 2019 meta-analysis of 13 RCTs, containing 127,477 participants, evaluated dose-dependent benefits of n-3 PUFAs in CVD events, and found that n-3 PUFA supplementation significantly lowered the CVD risk, and showed an inverse linear dose-response relationship in the range of 0 - 4,000 mg/d of n-3 PUFAs (Hu et al., 2019).

Diabetes mellitus (DM)

So far, various clinical trials have shown the beneficial effect of n-3 PUFAs in DM. Wang et al. (2003) measured the plasma fatty acid composition from 2,909 participants (aged 45 to 64) in a 9-year follow-up study, and found that n-3 PUFA levels were significantly lower in diabetics than in healthy
participants, suggesting a possible association between low n-3 PUFA levels and increased risk of DM. In 2004, a study examined the relationship between diet and type 2 diabetes (T2D) prevalence in the Nordic countries, and showed that lower T2D incidence was linked to higher dietary n-3 PUFA content (Thorsdottir et al., 2004). In 2011, an 8 to 9-year follow-up health study of 64,193 Shanghainese women, who were free of T2D, CVD, and cancer, reported that n-3 PUFA intake was inversely associated with T2D risk (Villegas et al., 2011). Similarly, a meta-analysis of 24 RCTs suggested a significant inverse correlation between n-3 PUFA intake and T2D risk in Asians, while n-3 PUFA content was dramatically lower in T2D patients than in healthy population (Zheng et al., 2012).

A 2013 study, which was designed to examine the effect of n-3 PUFAs on glucose metabolism in elderly T2D patients for 3-month, showed that those with n-3 PUFA supplementation had a lower fasting plasm glucose (FPG) level, haemoglobin A1c (HbA1c), remnant like particle (RLP), and apolipoprotein B (apo B) as compared to the control individuals, thus suggesting a significant improvement in impaired-glucose metabolism in elderly T2D patients (Ogawa et al., 2013). Similarly, Kurt et al. (2016) showed a significant decline in FPG, HbA1c, and pentosidase among T2D patients who received n-3 PUFAs (1.2 gm/day) for 2-month. A 2018 meta-analysis of 5 RCTs suggested that n-3 PUFA supplementation effectively reduced the level of FPG, insulin resistance (IR), and C-reactive protein (CRP) among patients with gestational diabetes, which occurs during pregnancy (Zhong and Wang, 2019).

Non-alcoholic fatty liver disease (NAFLD)

The beneficial effect of n-3 PUFAs in NAFLD has been supported by many clinical trials. In 2015, an RCT of 51 paediatric patients with NAFLD showed that n-3 PUFA supplementation for six months inhibited lipid accumulation as compared to the placebo group (Pacifico et al., 2015). Li et al. (2015) showed a significant reduction of plasma alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels in NASH patients who received n-3 PUFAs for six months, along with a significant reduction in TAG, CRP, and MDA levels. This study clearly showed that n-3 PUFAs can ameliorate impaired liver, and inhibit inflammation in NASH patients.

Recently, a meta-analysis of seven RCTs involving 442 patients on n-3 PUFAs effect on NAFLD showed that TAG, TC, and LDL-C levels were significantly reduced in the n-3 PUFAs group as compared to the control group; meanwhile, significant reduction of ALT, AST, and GGT was also noticed as a secondary effect which attenuated fatty liver and fibrosis (He et al., 2016). Similarly, a meta-analysis of four RCT involving 263 children with NAFLD demonstrated that n-3 PUFAs inhibited the progression of hepatic steatosis (Chen et al., 2018). Another meta-analysis of eight RCTs involving 1424 participants with NAFLD showed that n-3 PUFA supplementation reduced liver fat, and improved liver function (Yan et al., 2018). A 2018 meta-analysis of 11 RCTs showed that 1 gm/day supplementation of n-3 PUFAs in NAFLD patients resulted in 3.14 U/L, 2.43 U/L, 2.74%, and 9.97 mg/dL decline in the levels of ALT, AST, liver fat, and TAG, respectively (Guo et al., 2018). Although many studies showed the protective ability of n-3 PUFAs in NAFLD patients, larger scale and longer follow-up studies are needed to further validate these results.

Conclusion

Hypertriglyceridemia has become a prevalent disease due to high-fat diet and less exercise in the modern society. High TG level is a serious risk factor that enhances the incidence of CVD, DM, and NAFLD. In addition, high TG levels can promote inflammation and oxidative damage, which can aggravate the progression of the diseases. Several recent studies, including human clinical trials, suggest that n-3 PUFA supplementation can ameliorate these risks. It is speculated that n-3 PUFAs alleviate inflammation and oxidative stress by downregulating the activity of NF-κB and Nrf2. Besides, n-3 PUFAs reduce TG level by inhibiting synthesis or enhancing the clearance of TG. Based on these findings, one can suggest that n-3 PUFA supplements or n-3 PUFA-rich marine-derived foods can have beneficial health effects, and therefore should be included in the daily diet.

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