$PM_{2.5}$-induced Cardiovascular Health Effects and Potential Therapeutic Mechanisms of Omega-3 Fatty Acid Supplementation: A Scoping Review

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ABSTRACT

Hunt, Kirstin Lynn. $PM_{2.5}$-induced Cardiovascular Health Effects and Potential Therapeutic Mechanisms of Omega-3 Fatty Acid Supplementation: A Scoping Review (Under the direction of Dr. Jennifer Richmond-Bryant).

Recent studies have found that long-term exposure to air pollution, especially particulate matter (PM), was associated with increased morbidity and mortality. The peer-reviewed literature has shown that short-term exposure to $PM_{2.5}$ (PM < 2.5 μm) can cause adverse cardiovascular effects and mortality. The mechanisms by which $PM_{2.5}$ can initiate adverse cardiovascular health effects are still being investigated, but evidence suggests that inflammation, oxidative stress, and modulation of the cardiac autonomic nervous system (ANS) play a prominent role in vascular and endothelial dysfunction. Dietary supplementation with omega-3 fatty acids (O3FAs), including fish oil, have been found to reduce the risk of cardiovascular disease through anti-inflammatory and antioxidant mechanisms. Growing scientific evidence suggests supplementation with O3FAs, including fish oils, could protect against the adverse effects of $PM_{2.5}$. This scoping review aims to highlight the current scientific studies purporting that O3FA supplementation can mitigate the adverse effects of $PM_{2.5}$. An initial search of PubMed and Web of Science was conducted on January 31, 2021, with no date or location restrictions. A constraint included only papers published in English. The author supplemented this by searching reference lists of articles and performing a grey literature search on Google Scholar. Eligibility criteria were defined by a Population Exposure Comparison Outcome (PECO) statement to develop the study question and to aid in the selection process. The PECO framework included populations of human, animal, and *in vitro* systems with exposures to PM, $PM_{2.5}$, $PM_{10\text{-}2.5}$, concentrated ambient PM, diesel particulate matter, and black carbon. Comparison populations were supplemented with O3FAs or fish oil, but not limited to

combinations with other supplements. Outcomes included cardiovascular diseases, vascular effects, and endothelial function. Twelve studies were identified that met the eligibility criteria. Eleven of the 12 studies observed protective cardiovascular health benefits from supplementation with O3FAs after $PM_{2.5}$ exposure, including reduced inflammation and oxidative stress biomarkers. However, one study found that olive oil supplements improved endothelial function instead of fish oil. This review did not compare the studies' supplementation dosage of O3FAs or fish oil. Further research is needed to address the supplementation of fish oil to determine the optimum dosage for protection. This review suggests supplementation with O3FAs could be a cost-effective way to protect against cardiovascular injury due to $PM_{2.5}$ exposure.

DEDICATION

I want to dedicate my professional project to my dear mother, Susan Hunt, and in memory of my late father, William Hunt. Although he was my inspiration in continuing my education, my father was unable to see me complete my degree.

BIOGRAPHY

Kirstin was born in Chicago, Illinois, but grew up primarily in Chapel Hill, North Carolina. She received her undergraduate degree from the University of North Carolina at Chapel Hill (UNC-CH) in the Bachelor of Science in Public Health Program in Environmental Health Sciences and a minor in Women's Studies in 2007. After graduation, she began work at the Institute for Environment at UNC-CH.

Alongside her love for the environment, food and cooking have always been a significant part of her life. After leaving the Institute for Environment, Kirstin pursued a 12-year career as a Specialty Food Buyer at a gourmet food store, giving her the opportunity to travel the world discovering new and unique food products. After leaving the position a few years ago, she started a chocolate business with her mentor of 12 years, bringing specialty chocolate from independent European producers to the US. In 2020, Kirstin wanted to pursue a master's degree in environmental assessment to expand her undergraduate education and pursue a new career. She currently lives with her four beautiful cats in Durham, North Carolina.

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Chapter 1: Introduction

Ambient air pollution is emerging as one of the greatest global health problems, especially in sensitive population groups and areas experiencing high levels of air pollution.[1–4] Epidemiological studies have demonstrated a strong relationship between air pollution exposure and increased morbidity and mortality.[2,5] Furthermore, particulate matter (PM) is especially detrimental to human health, including damage to the cardiovascular and pulmonary systems and increasing mortality.[1] PM is classified by the size of the mass median aerodynamic diameter, including super-coarse (>10 μm), coarse $PM_{10-2.5}$ (2.5-10 μm), fine $PM_{2.5}$ (<2.5 μm), and ultrafine (UFP) (<0.1 μm).[6] PM_{10} is composed mainly of dust and biological material, while $PM_{2.5}$ comes from combustion operations, including car exhausts and the burning of fuels.[6]

Super-coarse PM and PM_{10} will generally get caught in the mouth and upper airways of the body and can be readily removed by mucociliary clearance, a defense mechanism composed of the mucous layer and cilia that can push inhaled PM and pathogens out of the airways.[1,7,8] $PM_{2.5}$ and UFP can penetrate the lung alveoli and directly translocate into the circulatory system, allowing it to cause adverse health effects throughout the body.[7] The definitive $PM_{2.5}$ mechanisms that cause adverse cardiovascular effects are still being investigated, but evidence suggests that systemic inflammation, oxidative stress, and modulation of the cardiac autonomic nervous system (ANS) play prominent roles in vascular and endothelial dysfunction.[9,10]

In the recent Integrated Science Assessment (ISA) for PM finalized in December 2019, a causal relationship was shown to exist between short-term exposure to $PM_{2.5}$ and cardiovascular health effects based on the epidemiological, toxicological, and controlled human exposure evidence.[10] Outcomes associated with short-term $PM_{2.5}$ exposure include emergency department (ED) visits and regular hospital admissions for exacerbation of ischemic heart disease (IHD) and

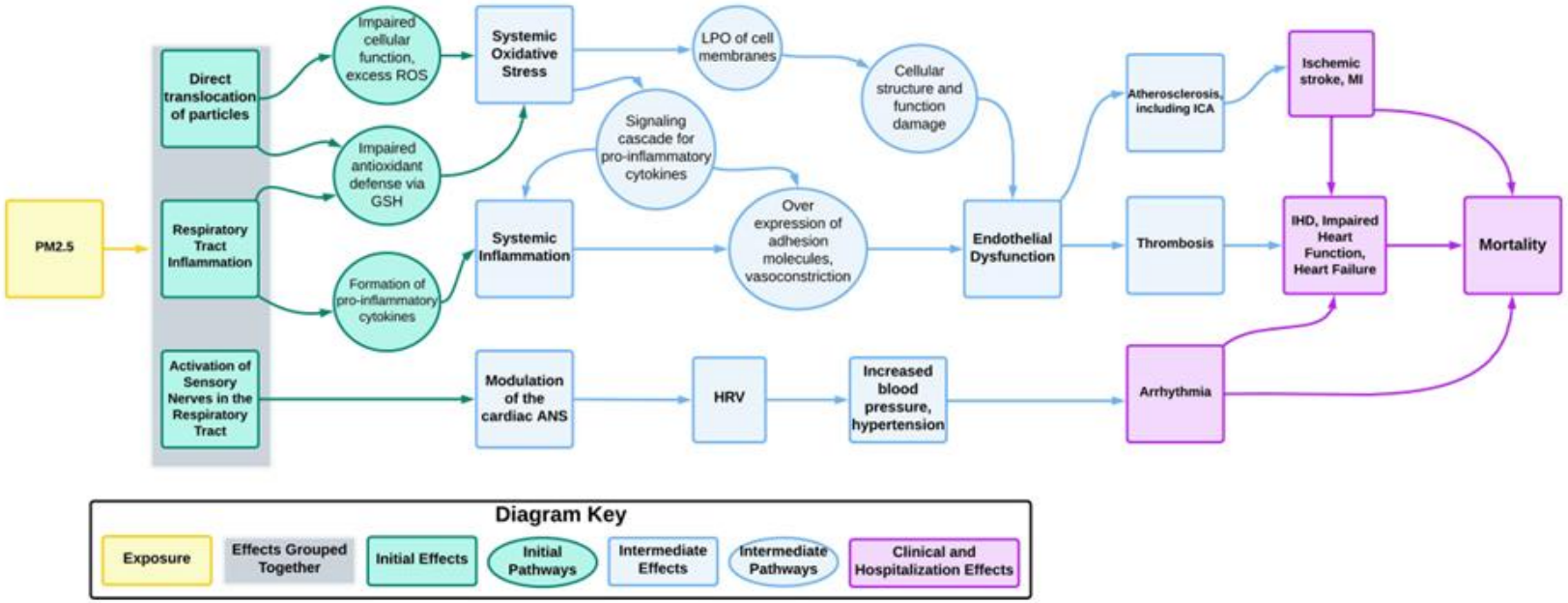
myocardial infarction (MI), heart rate variability (HRV), impaired vascular function, arrhythmia, stroke, increased blood pressure and hypertension, thrombosis, and other combinations of cardiovascular-related ED visits and hospital admissions, including cardiovascular-related mortality.[10] The evidence for long-term exposure to $PM_{2.5}$ suggests a more prominent association with mortality from cardiovascular disease, particularly IHD, and morbidity, especially in individuals with pre-existing conditions.[10,11] Long-term exposure to $PM_{2.5}$ health outcomes include atherosclerosis, HRV, decreased endothelial function, stroke, impaired heart function, and heart failure, as well as others previously mentioned in the short-term outcomes.[10]

Oxidative stress is thought to be a mechanism by which $PM_{2.5}$ induces adverse cardiovascular effects (Figure 1).[1] Oxidative stress can be described as an imbalance in the reactive oxygen species (ROS) / reactive nitrogen species (RNS) ratio and the body's capability to combat this action using antioxidant protective systems.[12,13] ROS are produced within the body during normal cellular metabolism and can be activated by exogenous environmental factors, including $PM_{2.5}$ exposure.[12,14] ROS are highly reactive molecules with unpaired electrons in the outer shell of their molecule.[14] Low levels of ROS can mediate the inflammatory response of cells that fight off infections or repair injury.[14] If the body's natural antioxidant defenses are overwhelmed and cannot maintain a balanced state, oxidative stress can damage cell structures and functions, including harm to DNA, lipid membranes, and other proteins.[15]

Inflammation, which can be induced by oxidative stress, is an integral part of the body's defense mechanism against injury and infection but can be damaging (Figure 1).[1] $PM_{2.5}$ is thought to induce adverse cardiovascular health effects via inflammatory pathways, particularly by the formation of pro-inflammatory cytokines, such as interleukin 6 (IL-6), interleukin 8 (IL-8), interleukin-1β (IL-1β), tumor necrosis factor α (TNF-α), and C-reactive protein (CRP).[16,17]

Pro-inflammatory cytokines are produced primarily by macrophages, a type of white blood cell that kills exogenous microorganisms, and are small proteins that aid in inflammatory reactions in the body.[18] Furthermore, inflammation and oxidative stress play an essential role in endothelial dysfunction, leading to cardiovascular health effects like atherosclerosis and thrombosis (Figure 1).[19] Endothelial cells within the vascular endothelium line arteries, veins, and capillaries and act as a barrier between blood and tissues within the body while controlling vascular relaxation and constriction, as well as adhesion molecules in the blood (e.g., ICAM-1 and VCAM-1).[20] During endothelial dysfunction, damage to endothelial cells via inflammation or oxidative stress may trigger the up-regulation of adhesion molecules, increased cytokine production from inflammation, and impaired vasodilation due to nitric oxide (NO) deficiency.[21] Endothelial dysfunction is thought to be a major mechanism by which atherosclerosis occurs.[19,21]

Additionally, studies have reported that $PM_{2.5}$ exposure can lead to modulation of the cardiac ANS, resulting in increased blood pressure and hypertension (Figure 1).[10,22] Moreover, the modulation of ANS can result in decreased HRV, which signifies the time variation between successive heartbeats and the ratio between the sympathetic and parasympathetic systems.[23–25] Two measurements of HRV include low-frequency (LF) power (0.04–0.15 Hz) and high-frequency (HF) power (0.15–0.40 Hz), each reflecting the sympathetic nervous system (i.e., "fight-or-flight" response) and parasympathetic nervous system (i.e., "rest and digest"), respectively.[25–27] Once $PM_{2.5}$ activates the ANS modulation, a shift towards sympathetic tone may occur, evidenced by changes in HRV.[10] Decreased HRV has been used as a risk factor for cardiac arrhythmias, MI, and even sudden death.[28] HRV measurements may provide another insight into the mechanistic pathways of $PM_{2.5}$ exposure.



PM2.5 = particulate matter with a mean aerodynamic diameter less than or equal to 2.5µm; GSH = glutathione; ROS = reactive oxygen species; LPO = lipid peroxidation; MDA = malondialdehyde; ANS = autonomic nervous system; HRV = heart rate variability; ICA = intracranial atherosclerosis; MI = myocardial infarction; IHD = ischemic heart disease.

Figure 1. Potential biological pathways of cardiovascular effects from PM2.5 exposure

The boxes denote the potential effects and outcomes discussed in the controlled human exposure and toxicological studies discussed in this review. The 2019 ISA on PM2.5 was also influential in the development of this figure.[10] The gray shaded area indicates that effects are grouped and can impact different biological pathways. Circles represent the biological pathways and biomarkers highlighted in these studies. The progression of effects is mainly from left to right. Color code: yellow = exposure; green = initial effects and pathways; blue = intermediate effects and pathways; purple = clinical and hospitalization effects.

An innovative study by Bang et al. on Greenland Eskimos in 1971 paved the way for public and scientific interest in the significance of a diet in marine fish, which is high in omega-3 fatty acids (O3FAs), and the association of lower incidence of IHD, a term given to adverse health effects caused by narrowing of heart arteries.[29,30] Since then, there has been growing scientific evidence that O3FA dietary supplementation, including fish oils or a diet high in oily fish, can protect against adverse cardiovascular effects.[31–33] This scoping review highlights the current scientific studies, including animal toxicity studies, *in vitro* studies, human exposure panel studies, controlled human exposure studies, and clinical trials, purporting that O3FA supplementation can reduce the adverse effects of PM exposure. Most papers cited in this review focus on $PM_{2.5}$. O3FAs are polyunsaturated fatty acids with a carbon-carbon double bond located at three carbons from the methyl end of the chain and are considered essential fatty acids, signifying that the body cannot synthesize them.[34] Thus, O3FAs must be consumed in the diet or supplemented. O3FAs have an essential function in cell membranes and cell receptors.[34] There are three major types of O3FAs, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are marine-derived O3FAs and are usually found in variable levels in fish oil supplements, and alpha-linolenic acid (ALA) which is found in vegetable oils and nuts.[30,34] Specifically, EPA and DHA have been found to reduce the risk of cardiovascular diseases through various mechanisms, including anti-inflammatory, antioxidant, and modulation of membrane phospholipids.[32,35] A recent systematic review and meta-analysis reported that O3FA intake could enhance the body's antioxidant defense against ROS by increasing total antioxidant capacity (TAC) and glutathione peroxidase (GSH-Px) activity and decreasing malondialdehyde (MDA).[12] Furthermore, evidence exists that O3FAs can counteract the release of pro-inflammatory cytokines (e.g., IL-6, IL-8, IL-1β, TNF-α, and CRP) in vascular tissues, helping to

restore vascular health.[32] Since endothelial cells are susceptible to oxidative stress, it has been suggested that supplements high in antioxidant properties, such as O3FAs, may protect the vascular endothelium from damage.[36] Furthermore, it may increase the availability of nitric oxide (NO), a compound that stimulates vasodilation, assisting regular endothelial function.

Over the last two decades, several reviews have addressed the health impacts of PM and whether diet and supplements of nutrients could modify PM-induced harmful effects on cardiovascular and pulmonary health.[9,14,37–39] A 2015 review on human clinical trials in which methyl nutrients (i.e., folate, vitamins B6 and B12, and methionine), vitamin C and E, and marine-derived O3FAs (i.e., fish oil, DHA, and EPA) were given as interventions for the detrimental health effects of air pollution, found that a balanced, healthy diet with micronutrient supplementation may help prevent the development of cardiovascular diseases due to air pollution.[38] In a non-systematic literature review, Barthelemy et al. reviewed only clinical studies and evaluated antioxidant-rich diets (i.e., the Mediterranean diet) and antioxidant supplementation (i.e., fish oil) to mitigate the adverse health effects of traffic-related air pollution.[14] In an earlier review from 2008, Romieu et al. studied the biological and epidemiological evidence of oxidative stress as a significant health effect of ozone and $PM_{2.5}$ air pollution and whether supplementation of antioxidant nutrients, vitamin C and E, β-Carotene, and O3FAs could protect and enhance the body's antioxidant defenses.[37] However, there is a need for an up-to-date literature review that collectively examines animal toxicity studies, *in vitro* studies, human exposure studies, and clinical trials that focus on O3FA supplementation as an intervention against the adverse cardiovascular health effects of $PM_{2.5}$. In this scoping review, the author evaluates the existing scientific literature on the potential for O3FAs to attenuate the adverse effects of PM on cardiovascular health.

Chapter 2: Methods

This paper follows the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) process.[40] However, as a single-author paper, it cannot be considered a systematic review because it needs more than one author to be considered "systematic" and instead will be defined as a scoping review.[41] The scoping review shares a comprehensive screening and selection process with the systematic review procedure but tends to offer a descriptive summary of a broader review topic.[42] In contrast, a systematic review provides a synthesis of evidence and assesses the risk of bias to address a specific question.[42] The detailed steps of electronic database searches are shown in the PRISMA flowchart (Figure 2).

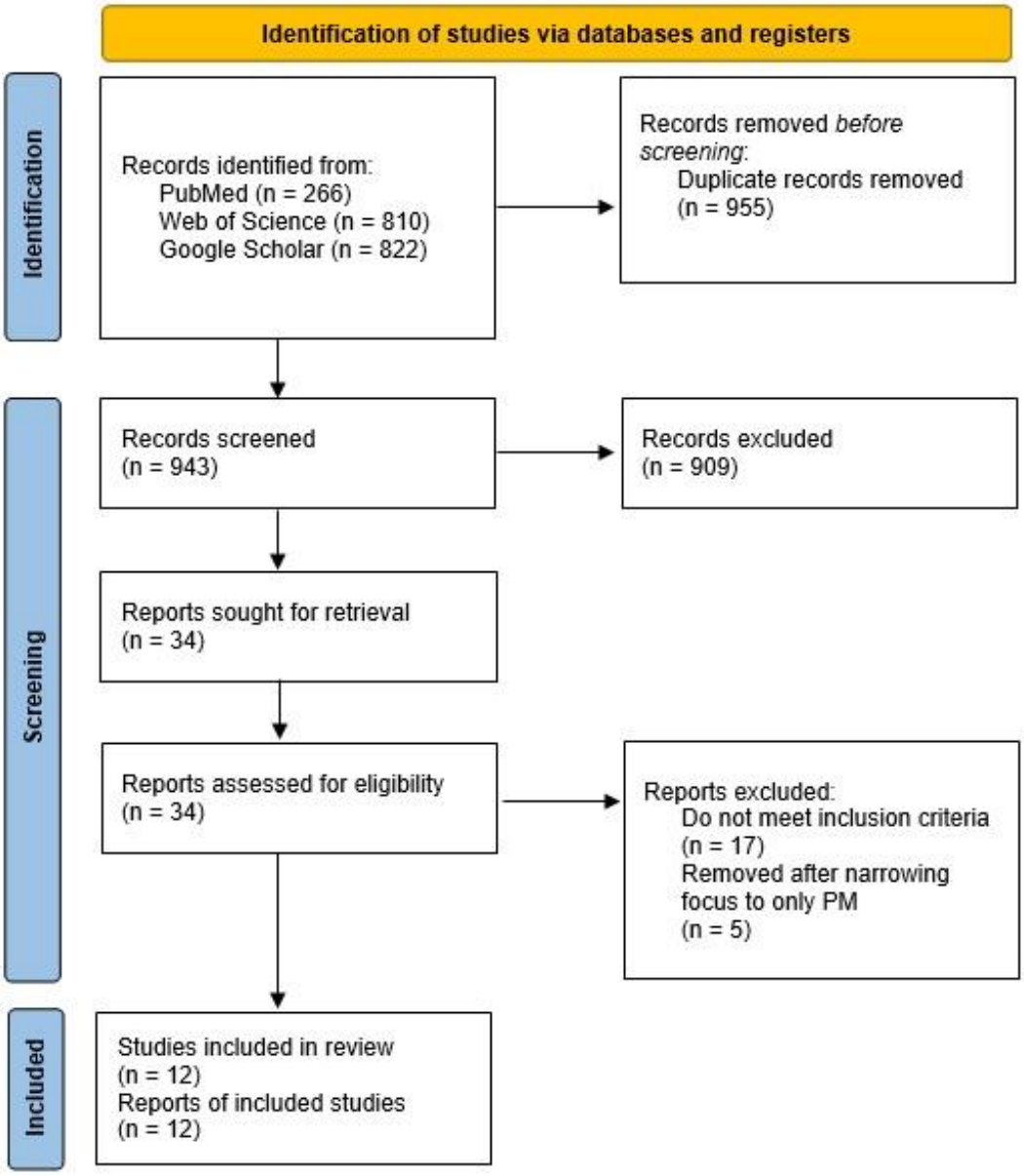


Figure 2. Flow diagram of the studies identified in this review.[40]

Literature Search

An initial search of PubMed (main search) and Web of Science (secondary search) were conducted on January 31, 2022. Relevant studies were obtained by using the following search terms: ((("Omega-3" OR "polyunsaturated fatty acid") AND ("Air pollution" OR "particulate matter" OR "PM" OR "PM2.5" OR "PM[2.5]" OR "PM_2.5" OR "ozone" OR "O3" OR "O[3]"

OR "[O_3]" OR "nitrogen dioxide" OR "NO2" OR "NO[2]" OR "NO_2")). The search was not limited by publication date. A total of 218 papers were originally found on PubMed, and 565 papers were initially found on the Web of Science. References were stored on RefWorks, and duplicates were removed. An updated search was performed for PubMed and Web of Science on May 17, 2022, to identify any new studies. An additional search term, "fish oil," was added to the initial list of terms. Forty-eight more papers were found, for a total of 266 papers, from PubMed. For Web of Science, 245 additional papers were found, for a total of 810 papers. Additionally, the author supplemented these findings by hand-searching cited references during the screening process for inclusion and performing a grey literature search on Google Scholar. No additional papers were found during this process. In September 2022, the focus of this review was narrowed to include only PM because limited literature was found on the therapeutic intervention of O3FAs and other criteria air pollutants, including NO_2 and O_3.

Eligibility Criteria and Screening Process

This paper included original studies published in English that evaluated the impacts of O3FA supplementation and reported associations of change in the adverse cardiovascular health effects due to exposure to ambient particulate matter, including $PM_{2.5}$. Outcomes of interest included:

- Cardiovascular effects include cardiovascular disease, elevated blood pressure and hypertension, atherosclerosis, HRV, IHD, MI, arterial stiffness, cerebrovascular diseases;
- Vascular effects, including platelet function, inflammation, and oxidative stress biomarkers;
- Endothelial function, including endothelial dysfunction, inflammation, and oxidative stress biomarkers.

All eligible papers included supplementation of O3FA or dietary intake of fish oil. Members of O3FA subfamily groups included EPA and DHA, primarily found in certain fish, and ALA, found in plant sources. Studies that included combined interventions with vitamin E (Vit E) and aspirin were found eligible, but only if combined with O3FA supplementation. No date limitations, location/setting restrictions, or age/population restrictions were included. Papers were excluded when the full text was not available.

The screening process was conducted in two parts to determine whether each individual article met the eligibility criteria. First, the author screened the original search from January 2022 by title, keywords, and abstract. Irrelevant articles were excluded, while prospective ones that mentioned air pollution, adverse health outcomes, and supplementation as an intervention were retained and were deemed "considered" and imported into an Excel document. The following information was extracted from each study: title, authors, publication year, country, journal name, DOI number, and study type [i.e., animal toxicity studies, *in vitro* studies, human exposure panel studies, controlled human exposure studies, clinical trials, epidemiology studies, or reviews]. A second screening process occurred where the full texts of the articles were reviewed to determine compliance with the eligibility criteria, excluding articles that did not fall under these specific elements of interest. The author consulted citation lists from the final batch of papers to check for any supplementary articles for inclusion.

PECO Criteria & Study Selection Process

A Population Exposure Comparison Outcome (PECO) statement design was used to develop the study question in this review to aid in the study selection process.[43,44] The following PECO study question was developed in relation to exposure to air pollution and O3FA supplementation intervention:

In any study population (P), how does supplementation with O3FA attenuate cardiovascular health effects (O) after exposure (E) to PM by comparison (C) groups taking supplements to placebo or blank groups?

Table 1. Inclusion criteria for each PECO domain

PECO	Inclusion Criteria
Population	• *Human* **:** Humans, without restriction on age, sex, or life stage • *Animal* **:** Experimental animals without restriction on species, age, sex, or life stage • *i n vitro* **:** Human or animal cells, tissues, or model systems
Exposure	Exposure to PM, **$PM_{2.5}$**, $PM_{10-2.5}$, concentrated ambient PM (CAP), diesel particulate matter (DPM), and black carbon (BC), • administered concentration • **controlled exposure** (i.e., controlled chamber and face mask) • **ambient monitoring data** (e.g., fixed site monitors and Mini-Vol portal air samplers) as an exposure surrogate • indirect measures such occupational history
Comparison	• *Human:* A comparison population supplemented with **O3FA** (including EPA, DHA, and ALA) or **fish oil**, but not limited to combinations with other supplements • *Animal:* Comparable animal populations that were treated with **O3FA** (including EPA, DHA, and ALA) or **fish oil**, but not limited to combinations with other supplements • *i n vitro:* Comparable cells or tissues exposure to **O3FA** (including EPA, DHA, and ALA) or **fish oil**, but not limited to combinations with other supplements
Outcome	• ***Cardiovascular health outcomes:*** CVD, blood pressure & hypertension, atherosclerosis, HRV, IHD, MI, atherosclerosis, arterial stiffness, cerebrovascular diseases • ***Vascular effects:*** platelet function, coagulation, inflammation, and oxidative stress biomarkers • ***Endothelial function:*** endothelial dysfunction, inflammation, and oxidative stress biomarkers

The PECO framework was used on the 34 remaining papers that were assessed for eligibility in the final screening process (Figure 1). Full texts were reviewed, an additional Excel document was created, and relevant information was extracted: title, authors, publication year, country of origin, population and sample size, exposure, comparison, outcome, and study type. A total of 12 papers remained after this process, and each paper was reviewed by the single author and evaluated based on the elements in Table 1.

After the study selection process, additional information was extracted from each paper and included in the Excel document. This information included whether the papers included a discussion of therapeutic mechanism(s) or an observed effect of O3FA supplementation or fish oil dietary intake. Additionally, conclusions from each study were included in the document, along with limitations addressed by the authors and potential biases. The author used the PECO framework in a way beyond the inclusion/exclusion criteria to encapsulate the main points of each paper. As a tool to summarize the facets of each paper, the PECO table helped the author to subdivide the papers and think about the therapy – fish oil or O3FA supplementation or divide by therapeutic mechanism.

Chapter 3: Results and Discussion

Short-term and long-term exposure may adversely affect human health through activating pathways mediating inflammation and oxidative stress, which lead to various severe morbidities, including endothelial dysfunction, HRV, arrhythmia, atherosclerosis, chronic cardiometabolic conditions, and even mortality.[45–48] Studies testing the therapeutic effects of O3FA have not fully explained all the mechanisms by which O3FA can mitigate the adverse cardiovascular health effects of $PM_{2.5}$ exposure.[49] However, the studies reviewed here indicate that mechanistic pathways may exist for protection. Accordingly, the findings from these studies predominantly describe observed effects versus therapeutic mechanisms of O3FA supplementation protection. This section is organized to concisely present these findings, with the following subsections: 1) antioxidant mechanisms, 2) anti-inflammatory pathways, 3) improvement of endothelial function, and 4) prevention of cardiac ANS modulation, including reduced HRV. The aim is to provide a framework for future research in reducing $PM_{2.5}$ health effects and the potential benefits of using dietary supplementation to mitigate the adverse impacts of $PM_{2.5}$ exposure.

Study Characteristics

Twelve studies have been included in this review that fit the inclusion criteria and addressed the study question, as outlined in the PECOS table (Table 1). Three were animal toxicity studies, two were cell toxicity studies using human umbilical vein endothelial cells **(**HUVECs), four were human exposure panel studies, two were controlled human exposure studies, and one was a clinical trial. Sample sizes in human exposure studies ranged from 29 to 135 participants, with various age groups, including 'healthy' college students to nursing home residents (>60 years old).[24,27,50–54] The primary sources of O3FAs were DHA, EPA, and ALA, with fish oil (a combination of EPA and DHA) supplements being the predominant treatment.

Several studies used soy oil as the placebo containing the O3FA ALA.[27,54] The dose of O3FAs given in human exposure studies ranged from 2 g/day to 4 g/day. Becerra et al. investigated participants with Type II diabetes and administered a single dose of aspirin (81 mg/day) for seven days before discontinuing to follow up with a 28-day regimen of fish oil (4g/day), followed by a combined treatment of aspirin (81 mg/day) and fish oil (4 g/day).[52] Another two studies evaluated the combined effects of O3FA and Vit E against the adverse cardiovascular effects of PM.[16,55] The 12 studies included in this review were carried out in four different countries, including China, Iran, Mexico, and the United States.

Antioxidant

The literature suggests a relationship between $PM_{2.5}$ exposure, an increase in oxidative stress biomarkers, and adverse cardiovascular health effects.[37,45] The body's antioxidant defense systems include both enzymatic and nonenzymatic pathways.[15] One pathway includes the body's storage of a critical antioxidant, glutathione. Once these stores are used up, ROS can build up, and the cells will enter into a state of oxidative stress, triggering an increase in antioxidant enzymes, including copper/zinc (Cu/Zn) superoxide dismutase (SOD), manganese (Mn) superoxide dismutase (SOD), GSH-Px, and glutathione reductase (GSH), that limit the generation of ROS through transcription factors.[37] Moreover, excess ROS can cause signaling cascades in which pro-inflammatory cytokines (e.g., TNF-α, IL-6, and IL-8) will be released via transcription activations, including NF-κβ and activation protein-1 responses, linking inflammatory and oxidative stress pathways.[37] Many markers exist for oxidative stress, including the antioxidant enzymes previously mentioned, but one that has yet to be mentioned is lipid peroxidation (LPO). LPO is a process by which ROS attacks lipid structures containing carbon-carbon double bond(s), especially polyunsaturated fatty acids in cell membranes.[56] A common

LPO product is MDA.[56] It also appears that not only can $PM_{2.5}$ cause oxidative stress via activating ROS, but it may also inhibit the antioxidant enzymes (including Cu/Zn SOD, Mn SOD, GSH-Px, and GSH) through transcription factors.[37] However, a recent observational study hypothesized that supplements high in antioxidants, such as O3FAs, could be beneficial in mitigating these harmful effects of oxidative stress on cardiovascular health.[49] Supplements high in antioxidants are thought to reduce the generation of ROS, thus controlling the amount of glutathione used in response to oxidative stress and increasing the other antioxidant enzymes.[54] Figure 3 describes $PM_{2.5}$-induced cardiovascular effects and the potential protective pathway mechanisms of O3FAs. One way they are thought to offer protection from oxidative stress is by interfering in the oxidant metabolites' reactions by removing ROS and thus inhibiting other oxidation reactions by being oxidized.[57] In a recent systematic review and meta-analysis, the authors found that O3FA could be beneficial in the antioxidant pathways against ROS.[12] However, the underlying therapeutic mechanisms are still being investigated concerning air pollutants such as $PM_{2.5}$.

Several studies measured chemical biomarkers of oxidative stress after exposure to $PM_{2.5}$ and found evidence that O3FAs can act as antioxidants, interfering with oxidative stress pathways. Lin et al. evaluated two biomarkers of systemic oxidative stress, including oxidized low-density lipoprotein and LPO, and three biomarkers of antioxidant activity, including TAC, GSH-Px, and SOD, in serum levels in 65 healthy college students in Shanghai, China, in response to short-term exposure to $PM_{2.5}$.[50] They found that fish oil supplementation significantly decreased low-density lipoprotein and improved antioxidant activity. O3FA, particularly EPA and DHA found in marine-derived fish oil, have been found to reduce the generation of ROS through nicotinamide adenine dinucleotide phosphate-oxidase activity.[50]

These findings are consistent with another human exposure study that evaluated similar chemical oxidative stress biomarkers in nursing home subjects in Mexico City.[54] In this randomized controlled trial, Romieu et al. hypothesized that the mechanistic action of fish oil supplementation could mediate oxidative stress responses in the body by reducing the generation of ROS, regulating GSH levels, and increasing antioxidant enzymes.[54] First, in the pre-supplementation phase, they found decreased levels of antioxidants and antioxidant enzymes, including Cu/Zn SOD and GSH, and increased levels of LPO products in plasma samples in elderly test subjects after exposure to indoor $PM_{2.5}$.[54] Cu/Zn SOD(s) plays a critical part in reducing oxidative stress within target cells by preventing the formation of hydrogen peroxide (H_2O_2) from superoxide anion (O_{2-}).[54,58,59] This process happens when antioxidant enzymes interact with each other; once Cu/Zn SOD reduces O_{2-} to H_2O_2, GHS-Px converts it to H_2O.[59] Under normal, non-oxidative stress conditions, the body's endogenous antioxidants can process O_{2-} to prevent buildup. However, under oxidative stress states, the antioxidant enzymes may become inhibited, as demonstrated by Romieu et al. for the pre-supplementation phase with reduced levels of antioxidant enzymes (i.e., Cu/Zn SOD and GSH).[54] Exogenous antioxidants may provide the body with additional protection.[59] As Romieu et al. found in the supplementation phase, test subjects in the fish oil group were observed to have increased levels of the antioxidant enzyme Cu/Zn SOD and increased levels of GSH, providing support that exogenous antioxidant supplements, such as O3FA, act in a therapeutic mechanism pathway. Additionally, the fish oil group's LPO levels were significantly decreased in response to $PM_{2.5}$. Studies have shown that exogenous, supplemented antioxidants can protect against LPO.[59,60] A supportive study by Guan et al., using a rat intracranial atherosclerosis model, quantified several oxidative stress biomarkers, including ROS, MDA, and SOD, after inhalation exposure to $PM_{2.5}$

for 12 weeks.[61] They found that $PM_{2.5}$ induced cerebrovascular oxidative stress (shown by elevated levels of oxidative stress biomarkers ROS, MDA, SOD) and observed that O3FA significantly decreased ROS generation and MDA levels and increased SOD levels after exposure to $PM_{2.5}$.[61] In a recent observational study using a dietary questionnaire to screen participants, Chen et al. investigated the potential beneficial effects of dietary O3FA consumption (but not supplementation) against short-term exposure to $PM_{2.5}$ and ozone levels in healthy adults in the Research Triangle area of NC.[49] The authors discuss that since O3FAs, especially marine-derived DHA and EPA, contain carbon-carbon double bonds that can be oxidized, they may blunt oxidative stress pathways that can lead to arteriosclerosis and acute coronary syndrome. These supportive findings suggest that O3FAs act as antioxidants to intervene in $PM_{2.5}$-induced oxidative stress pathways.

Two studies looked at the separate and combined treatments of Vit E and O3FA, again offering support for underlying therapeutic antioxidant mechanisms. In a cell toxicity study, Bo et al. found that HUVECs treated with O3FA exhibited "significant antioxidant effects," particularly regarding increasing SOD levels after $PM_{2.5}$ exposure.[55] Moreover, the combined treatments of Vit E and O3FA demonstrated the significant capability of decreasing MDA and ROS levels in HUVECs, and still improved SOD activity, but not statistically significant. In a related animal toxicity study, Du et al. measured similar chemical biomarkers after separate (low, medium, and high doses) and combined treatments with O3FA supplements and Vit E, including SOD activity, GSH-Px, and MDA levels.[16] In the combined groups, MDA was significantly lower, while SOD levels were significantly higher, and GSH-Px showed significant improvement (i.e., increased activity) compared to separate treatment groups after $PM_{2.5}$ exposure. Like other studies, they found that exposure to $PM_{2.5}$ caused increased levels of MDA

and declines in SOD and GSH-Px activity, with treatment with Vit E and O3FA attenuating these harmful effects. Separate O3FA treatment was beneficial in medium and high doses but not in low doses. Furthermore, Du et al. found that a specific dosage of combined O3FA and Vit E treatment gave the greatest protection:10 mg/kg b.w. of Vit E and 30 mg/kg b.w. O3FA.

O3FAs, acting as antioxidant compounds, can potentially ameliorate the harmful $PM_{2.5}$ mechanisms that cause oxidative stress.[12] The key potential protective mechanisms include O3FAs' abilities to reduce ROS by interfering in oxidant metabolite reactions, increasing antioxidant enzymes, and lowering LPO of cell membranes (Figure 3). The literature furthermore implies that supplementation with O3FA may potentially protect against PM-induced adverse cardiovascular health effects caused by oxidative stress.[16,49,50,54,55,61]

Anti-inflammatory

As aforementioned, $PM_{2.5}$ is thought to induce adverse cardiovascular health effects via inflammatory pathways, particularly by forming pro-inflammatory cytokines, such as IL-6, IL-8, IL-1β, TNF-α, and CRP.[16,17] However, it is postulated that O3FAs can inhibit or at least partially inhibit inflammation pathways through several different mechanistic ways, including inhibition of pro-inflammatory transcription factors (i.e., nuclear factor β (NF-kB)), activation of anti-inflammatory signaling pathways (i.e., G protein-coupled receptor 120 (GPR120) and peroxisome proliferator-activated receptor gamma (PPAR-γ)), and developing anti-inflammatory pro-resolving mediators (SPMs) (i.e., resolvins, protectins, and maresins). [50,62] Each mechanism is described below (Figure 3).

$PM_{2.5}$ has been shown by *in vitro* studies to cause the expression of the pro-inflammatory transcription factor of NF-κβ.[63,64] NF-κβ is triggered through a signaling cascade from inflammatory stimuli, leading to the phosphorylation of an inhibitory subunit called Iκβ.[65] An

inhibitory subunit, such as Iκβ, is an enzyme complex that interferes with a transcription factor, in this case, NF-κβ, by binding to it and making it inactive.[66] Iκβ is then degraded after phosphorylation, allowing NF-κβ activation and translocation from the cytosol (i.e., inactive form) to the nucleus (i.e., the active form) of the cell, where it can upregulate gene expression of several pro-inflammatory pathways, including the increase of pro-inflammatory cytokines and regulation of adhesion molecules (i.e., ICAM-1 and VCAM-1).[65,67] Although inhibition of NF-κβ transcription factor was not comprehensively discussed in any study's results, two studies alluded to a possible O3FA therapeutic mechanism in their analysis. Sriram et al. discussed how O3FAs inhibit the activation of NF-κβ, suggesting that this could be a means by which they observed a reduction in inflammation cytokines.[68] In agreement with this hypothesis, Romieu et al. suggest that O3FA can block the NF-κβ pathway, decreasing PM-mediated inflammation.[54] Examining the effects of marine-derived O3FAs and the mechanisms associated with inflammation prevention, a recent review postulated two mechanisms that could explain the intervention pathways.[65] First, O3FAs may interact with the inhibitory subunit, Iκβ, and decrease the phosphorylation reaction. Second, O3FAs may interfere with NF-κβ through activation of PPAR-γ, an anti-inflammatory transcription factor.

Studies have also found that systemic inflammation was inhibited as long as sufficient levels of O3FA were present to activate functional GPR120.[69,70] In this review, two studies postulated that GPR120 activation might be a mechanistic pathway for O3FAs inhibiting inflammation.[16,55] Du et al. and Bo et al. found that their observations of decreasing levels of pro-inflammatory cytokines, including IL-6, after O3FA supplementation were consistent with findings from other papers that demonstrated that O3FAs have anti-inflammatory properties by activation of GPR120, citing papers from Wellhauser et al. and Oh et al., respectively.[16,55,69,70]

Wellhauser et al. utilized a cell model derived from the rat hypothalamus and found that cells pretreated with DHA, an O3FA derivative, did not exhibit inflammation responses upon exposure to the pro-inflammatory cytokine TNF-α. Furthermore, they suggest that GPR120 interrupts the inflammatory pathways, specifically Iκβ /NF-κβ, and hinders the downstream cascade of transcription factors for pro-inflammatory cytokines.[69,70] Similarly, Oh et al. showed that the GPR120 functions as the O3FA receptor and sensor in their animal toxicity study, using WT mice and GPR120 knockout mice.[69] They found that O3FA-treated WT mice did not show signs of inflammation, but O3FA-treated GPR120 knockout mice exhibited inflammation, implicating that O3FAs exert "robust and broad" anti-inflammatory signaling due to GPR120 and not another pathway.[69] Additionally, they hypothesized that pro-inflammatory signaling cascades (i.e., TNF-α) converge downstream of GPR120 activation.[69] A recent review suggests that these three mechanisms, inhibition of activating pro-inflammatory transcription factor NF-κβ, activation of anti-inflammatory transcription factor PPAR-γ, and binding to GPR120, are all interlinked, although the "full extent of this is not yet elucidated." [65]

A number of studies examined in this review investigated the levels of pro-inflammatory cytokines to evaluate the inflammation conditions after exposure to $PM_{2.5}$ and conjectured that O3FAs could decrease pro-inflammatory cytokine production; however, they did not describe exact intervention mechanisms. In an animal toxicity study, Guan et al. demonstrated that O3FA supplementation reversed the increases of IL-1β, IL-6, and TNF-α production after $PM_{2.5}$ exposure, especially for Sprague-Dawley rats fed a high-cholesterol diet.[61] In an earlier paper from the same primary author, similar conclusions were drawn with O3FA significantly reversing the levels of IL-6 and TNF-α (IL-1β was not measured).[71] In accord, human exposure studies also found that O3FA supplementation decreased cytokine production.[53,68] As already

suggested, inhibition of NF-κβ could explain why O3FAs can reduce cell surface expression of adhesion molecules, inflammatory cytokines, and cyclooxygenase (COX) enzymes.[65] In turn, these cytokines, especially IL-6, are reported to induce the transcription of CPR, an acute inflammatory protein.[72] Two studies looked at CRP as a critical biomarker for inflammation. Lin et al. found CRP levels lower in the fish oil group.[50]

In addition, O3FA supplementation may attenuate inflammation by the formation of specialized pro-resolving mediators (SPMs) called resolvins, protectins, and maresins.[65] The importance of SPMs in regulating inflammation has encouraged recent research into their therapeutic mechanisms in cardiovascular diseases.[73] Croft et al. and Barkhordari et al. suggest that O3FA's potential to derive potent anti-inflammatory SPMs could suppress the production of inflammatory cytokines.[53,74] In a double-blind, placebo-controlled clinical trial, Barkhordari et al. observed that O3FA supplementation caused a reduction of CRP, as well as TNF-α and IL-12, but was not significant compared to the placebo group.[53] Barkhordari et al. speculate that they may not have found a significant change because of the short time frame of O3FA supplementation (60 days) and the lower dosage (1000 mg fish oil) since other studies found significant decreases in CPR (and TNF-α).[75] In an observational study of the habitual dietary intake of O3FAs, Hao Chen et al. discussed these potent anti-inflammatory mediators as an important step in attenuating $PM_{2.5}$-induced inflammation.[49] Mechanistically, resolving mediators are enzymatically produced when marine-derived O3FAs (DHA and EPA) serve as substrates in the COX pathway.[73,76,77] SPMs then downregulate the inflammation process by reducing cytokine production and promoting tissue repair.[73] SPMs are well known to be anti-inflammatory and "inflammation resolving," inhibiting the production of cytokines, such as TNF-α and IL-1β.[65]

These findings reinforce O3FA's possible ability to inhibit pro-inflammatory transcription factors (i.e., NF-κβ), activate anti-inflammatory signaling pathways (i.e., PPAR-γ), and develop anti-inflammatory SPMs (Figure 3). However, more research is needed to find the links between these mechanisms and how O3FA exogenous supplementation reacts with all three. Other anti-inflammatory actions of O3FA have been proposed in other reviews, including O3FAs potential to alter cell membranes and disruption of lipid rafts.[65] However, these mechanisms were not addressed explicitly in the studies herein.

Endothelial Protection

Endothelial dysfunction is attributed to the early development stages of atherosclerosis and can be caused by increased inflammatory cytokine production and reduced vasodilation.[78] However, a recent review of epidemiology studies and clinical trials found that a combination of EPA and DHA, the major components of fish oil, was able to improve endothelial function (Figure 3).[79] Although the definite mechanisms of O3FA protection have not been entirely clarified, studies have shown that O3FA may improve endothelial function by activating endothelial nitric oxide synthase (eNOS) and increasing NO levels.[79] Additionally, O3FA may lower E-selectin, a selectin cell adhesion molecule activated by cytokines (e.g., TNF-α) in endothelial cells.[80] Several $PM_{2.5}$ exposure studies found consistent outcomes, demonstrating these underlying therapeutic mechanisms of O3FA supplementation.

Lin et al. shed light on several unique mechanisms for protecting endothelial function.[50] In this controlled human exposure study, O3FA supplementation was associated with considerable increases in endothelial function. The authors found that a biomarker of endothelial cell activation and neutrophil adhesion, E-selectin, was significantly decreased in participants who were supplemented with 2.5 g/day of fish oil. As the authors point out, O3FAs can

mechanistically reduce the impact of neutrophils and monocytes by decreasing the expression of vasoconstrictors, such as E-selectin. Further supported by another study. Nomura et al. studied the effects of EPA on E-selectin in hyperlipidemic patients with Type 2 diabetes mellitus and found that EPA treatment significantly lowered E-selectin.[81] This study did not look at protection against $PM_{2.5}$ but did identify potential mechanisms for EPA to improve endothelial function, including inhibition of platelet aggregation. However, the benefits of O3FA lowering the levels of E-selectin have been inconsistent. A meta-analysis of randomized controlled trials found no significant effects on E-selectin after O3FA supplementation, pooling results from 10 studies.[80] However, they did find that O3FA supplementation lowered ICAM-1 levels. They suggest that O3FA may only selectively inhibit ICAM-1, but not the others.

Additionally, Lin et al. found that eNOS was increased, although insignificantly.[50] eNOS is an enzyme that produces NO, a "vasoprotective molecule," and acts as a key shield for endothelial cells to fight off vascular attacks.[50] Previous studies have proposed that O3FAs can enhance NO production by modifying eNOS, indicating a clear mechanistic protection pathway.[55,78] It is important to note that Lin et al.'s study is not a controlled $PM_{2.5}$ study and instead estimated exposures based on fixed-site measurements on the campus. However, the study still suggests intervention mechanisms for O3FA supplementation. Endothelin-1 (ET-1) is another vasoconstrictor secreted by endothelial cells that act as the "natural counterpart of the vasodilator" NO and is enhanced by inflammatory cytokines and free radicals.[82] Sriram et al. assessed the major components of fish oil (i.e., DHA and EPA) and whether they could inhibit the release of ET-1 across two exposure time periods (24 hr. and 48 hr.).[68] They found that more than DHA, EPA was more effective at mitigating ET-1 release, suggesting a potential mechanism.[68] However, unlike the previous studies, Tong et al. found that fish oil supplements

did not have a beneficial endothelial response after controlled exposure to CAP, a high dose exposure to particle sizes 0.02 to 0.25 μm, in 42 middle-aged participants.[51,83] The study results found that instead, olive oil supplements attenuated the harmful effects on endothelial function after exposure. The authors did not investigate the mechanism by which olive oil supplementation could offer protection, but they speculated that the anti-inflammatory and anti-oxidant properties of oleic acid, a bioactive component of olive oil, could be the answer.[51] Both O3FA and olive oil, principally oleic acid, are known for their antioxidant and anti-inflammatory properties.[14] The authors offer several limitations to their study, including the small sample size and the fact that the exposure to concentrated PM and air was not randomized.[51]

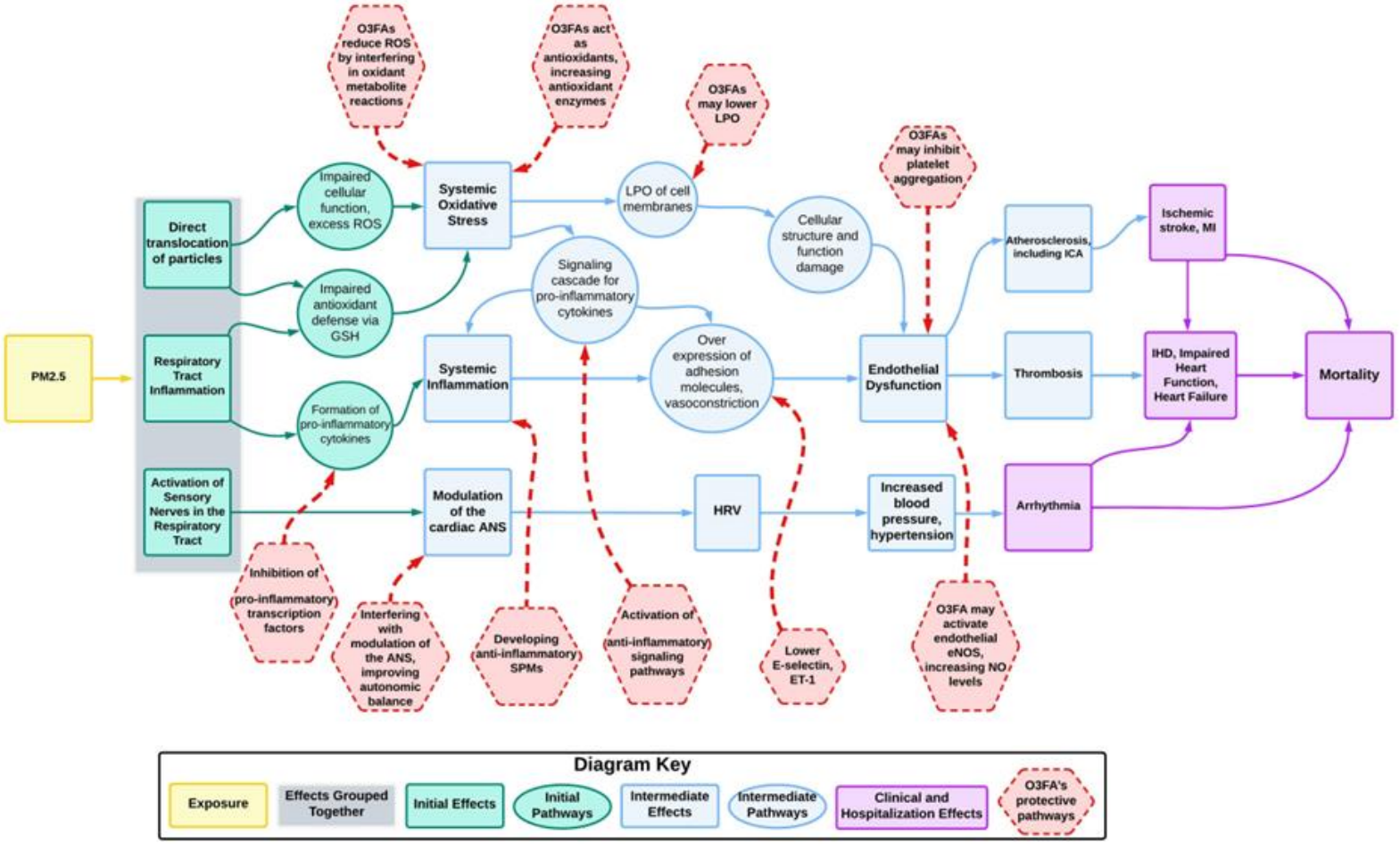
Inflammation and oxidative stress have been shown to play a role in endothelial dysfunction and the development of thrombosis and atherosclerosis progression, including intracranial atherosclerosis (ICA).[84,85] In a panel cohort study, a protective outcome was observed after combined treatment with fish oil and aspirin blunted the effects of $PM_{2.5}$ on platelet function and thromboxane B2, a vasoconstrictor and platelet aggregating agent, in patients with type 2 diabetes mellitus.[52] Platelet aggregation and increased thromboxane B2 production can lead to vascular injury, ultimately leading to thrombosis.[86] Thromboxane B2 is produced by the COX enzyme pathway from a precursor (i.e., arachidonic acid), while EPA is known to compete with arachidonic acid in this pathway.[52] The.[52] In an animal toxicity study, Guan et al. investigated the effects of $PM_{2.5}$ exposure on the process of ICA development in adult Sprague-Dawley rats.[71] Finding that inhalation exposure to $PM_{2.5}$ for 12 weeks can induce ICA, including middle cerebral artery (MCA) thickening and MCA lumen narrowing, they further investigated whether O3FA supplementation would ameliorate these damaging effects. They found that O3FA supplementation by gavage (5 mg/kg/day) significantly mitigated the decreased MCA lumen

diameter and increased media thickness, especially after 12-week exposure to $PM_{2.5}$. Concerning vascular endothelial dysfunction, they investigated the expression of VCAM-1 and inducible nitric oxide synthase (iNOS). Once again, they observed that O3FA supplementation significantly decreased the mRNA expressions of both biomarkers. Like other previous studies, Guan et al. discovered that O3FA supplementation also reversed the elevated expressions of inflammation cytokines, specifically IL-6 and TNF-α. In a later study by the same primary author, Guan et al. again used an ICA model in rats to look at the roles of systemic inflammation and oxidative stress on MCA morphology due to exposure to $PM_{2.5}$ and whether O3FA supplementation could mitigate these processes.[61] Expanding on their previous study, they looked at the role $PM_{2.5}$ has in inducing ICA. In adult Sprague-Dawley rats, 12 weeks of exposure to a daily mean of 44 $\mu g/m^3$ concluded with the diagnosis of atherosclerosis in the MCA. Overall, their findings were consistent with their previous study, finding that omega-3 fatty acids can protect against ICA development.

Prevention of Modulation of the Cardiac ANS, including HRV

Reduced HRV (also called increased LF HRV), an indicator of poor cardiovascular autonomic function, has been associated with air pollution, specifically, $PM_{2.5}$.[87,88] Several studies considered whether O3FAs could reverse the harmful effects of $PM_{2.5}$ on reducing HRV (Figure 3). In a randomized, double-blind trial, Romieu et al. provided 50 nursing home residents (>60 years of age) exposed to high levels of $PM_{2.5}$ indoors in Mexico City with 2 g/day of fish oil or 2 g/day of soy oil and measured HRV for a six-month observation period.[27] They found that significant protection was observed in the group taking fish oil, but only a small decrease in $PM_{2.5}$-induced reduction in HRV was seen in the soy oil group. In a later study, Romieu et al. hypothesized that the mechanism by which $PM_{2.5}$ reduces HRV is oxidative stress, and thus

O3FA could modulate the adverse effects on HRV by acting on the oxidative stress pathways.[54] However, according to the recent ISA, the mechanism for the modulation of ANS remains unclear.[10] Romieu et al. evaluated whether O3FA supplementation could protect against the cardiac alterations linked to $PM_{2.5}$ exposure, including reduced HRV and previously discussed oxidative stress biomarkers (Cu/Zn SOD activity, GSH-Px, and LPO products).[54] Indoor $PM_{2.5}$ levels were inversely related to Cu/Zn SOD activity, increased lipid oxidation products, and decreased GSH levels. They found that participants in the fish oil treatment group significantly increased Cu/Zn SOD activity and GSH levels.[54]-In a short-term (2-hr) CAP-controlled exposure study, subjects were supplemented with either fish oil (3 g/day) or olive oil (3 g/day) for four weeks.[24] Tong et al. found that participants taking olive oil supplements showed significant modulation of the cardiac ANS, evidenced by the increased LF-HRV and decreased HF/LF ratio.[24] However, fish oil supplementation appeared to attenuate these CAP-induced changes. Tong et al. postulate that O3FA may improve the autonomic balance by interfering with $PM_{2.5}$-induced ANS modulation, which increases the sympathetic nervous activity (Figure 3).[24]



PM2.5 = particulate matter with a mean aerodynamic diameter less than or equal to 2.5µm; GSH = glutathione; ROS = reactive oxygen species; O3FA = omega-3 fatty acid; LPO = lipid peroxidation; MDA = malondialdehyde; ANS = autonomic nervous system; HRV = heart rate variability; ICA = intracranial atherosclerosis; MI = myocardial infarction; IHD = ischemic heart disease.

Figure 3. $PM_{2.5}$-induced cardiovascular health effects and potential therapeutic mechanisms of O3FA

This diagram is based on Figure 1. Red-shaded hexagon shapes represent O3FA's potential protective mechanisms, with red-dotted line arrows indicating the targets of inhibition and interference.

Chapter 4: Conclusion

A recent systematic review meta-analysis found that long-term exposure to $PM_{2.5}$ and PM_{10} was associated with increased mortality, especially with $PM_{2.5}$, and the relationships remained at even low exposure levels.[89] Although lowering $PM_{2.5}$ levels is an ultimate goal for global health, it may not be a feasible solution for the near future due to anticipated climate change impacts. Thus, other alternatives should be explored to protect human cardiovascular health. Diet and supplements may provide a sensible solution to protecting human health and assisting in future disease prevention strategies.

Eleven of the twelve studies discussed in this review suggest that O3FA supplementation protects against the damaging cardiovascular effects of PM exposure. However, further studies are needed to better understand the therapeutic mechanistic pathways by which O3FAs can defend the cardiovascular system. Furthermore, an important concern in any dietary supplementation is the appropriate dose. The U.S. Food and Drug Administration recommends consuming no more than 5 g of combined EPA and DHA per day.[90] This scoping review did not evaluate the dosage amounts of O3FA or fish oil supplements in each study, nor did it efficiently evaluate the ratio amounts of the major types of O3FAs (EPA, DHA, and ALA) in fish oil. Additionally, one study found that test participants given olive oil supplements instead of fish oil supplements experienced improved endothelial function after exposure to concentrated particulate matter.[51] An earlier study by two of the primary authors found that fish oil weakened PM-induced acute cardiac changes, including increased LF HRV, but olive oil did not.[24] Nevertheless, olive oil should be further investigated as a possible intervention strategy.

This scoping review focused on O3FA supplementation as a strategy to mitigate the adverse cardiovascular health effects but also included several studies with additional

supplements. Two toxicity studies examining combined O3FA and Vit E supplementation found reduced inflammation and oxidative stress biomarkers due to $PM_{2.5}$ in their test populations. An additive effect was observed when both Vit E and O3FA supplements were combined in treatment, especially in decreasing the production of IL-1β. These studies hint that an appropriate combined dosage could protect human populations from $PM_{2.5}$-induced inflammation and oxidative stress.[16,55] However, a lung toxicity study found that Vit E did not significantly affect $PM_{2.5}$-induced inflammatory changes or oxidative stress.[91] Further research is needed to discover the correct dose of each nutrient that will yield the greatest protection for human subjects. Overall, supplementing both O3FA and Vit E could be a cost-effective way to protect against cardiovascular injury in humans.

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APPENDICES

Appendix A

Table 1A. Main characteristics of the included studies

Title	Authors / Publication Year	Country/ Place	Study Design	Population	Exposure	Comparison	Outcome	Results	Study Conclusions	Notes/Gaps
Cardiovascular Benefits of Fish Oil Supplementation Against Fine Particulate Air Pollution in China	Lin et al., 2019	Shanghai, China	**Human Exposure Panel Study** [Randomized, Double-Blinded, Placebo-Controlled]	65 adults (healthy college students aged 20 to 25 years old)	PM2.5 concentrations (avg. 38 μg/m^3) were measured in real-time from fixed sites on campus.	Randomly assigned to the fish oil group (2.5 g/day) or the placebo group given sunflower-seed oil (2.5 g/day).	Cardiovascular health biomarkers include systemic inflammation, coagulation, endothelial function, and oxidative stress.	The fish oil group was observed to be beneficial for 5 biomarkers of blood inflammation, coagulation, endothelial function, oxidative stress, and neuroendocrine stress.	Participants in the O3FA supplementation group were observed to have short-term cardiovascular benefits after $PM_{2.5}$ exposure.	Estimation of $PM_{2.5}$ exposures via an outdoor monitor on campus. • Only healthy young adults were used in the trial, which, compared with sensitive populations (i.e., older adults), may not be as susceptible to the adverse effects of air $PM_{2.5}$.
The Effect of Supplementation with Omega-3 Polyunsaturated Fatty Acids on Markers of Oxidative Stress in Elderly Exposed to PM2.5	Romieu et al., 2008	Mexico City, Mexico	**Human Exposure Panel Study** [Randomized, Double-Blinded, Placebo-Controlled]	52 adults (nursing home residents older than 60 years old)	Daily 24-hr measurements of ambient PM2.5 indoors via Mini-Vol portal air samplers and outdoors via a fixed monitor on the roof.	Randomly assigned to either fish oil (2 g/day) or soy oil (2 g/day) as the control for the 4-month supplementation phase. A pre-supplementation phase occurred for 3 months.	Vascular effects, including oxidative stress biomarkers (Cu/Zn SOD, LPO, and GSH).	Supplementation of O3FA appeared to attenuate the negative effects of PM2.5 on biomarkers, including an increase in Cu/Zn SOD activity and GSH plasma levels.	Supplementation with O3FA appeared to modulate the adverse effects of PM2.5 on oxidative stress biomarkers.	Exposure assessment was limited to 24-hr stationary Mini-Vol portal air samplers of $PM_{2.5}$ indoors.
PM2.5 Exposure Induces Systemic Inflammation and Oxidative Stress in an Intracranial Atherosclerosis Rat Model	Guan et al., 2019	Beijing, China	**Animal Toxicity Study**	54 male Sprague-Dawley rats (6 weeks old)	Rats were exposed to ambient $PM_{2.5}$ using a versatile aerosol concentration enrichment system in a controlled chamber.	Randomly divided into 3 groups: a normal chow diet, a high-cholesterol diet with O3FA supplementation (5 mg/kg/per day), or a high-cholesterol diet.	Vascular effects, including MCA morphology (measured by the thickness of the MCA and luminal diameter), systemic inflammation (TNF-α, IL-6, IL- 1β, and IFN-γ), and cerebrovascular oxidative stress (ROS, MDA, and SOD).	O3FA supplementation attenuated PM2.5-induced systemic inflammation, vascular oxidative stress, and ICA.	O3FA dietary supplementation is capable of ameliorating $PM_{2.5}$-induced systemic inflammation, preventing ICA development.	Nutrients were given by lavage, thus not representative of human supplementation.
Combined Effects of Vitamin E and Omega-3 Fatty Acids on Protecting Ambient PM2.5- Induced Cardiovascular Injury in Rats	Du et al., 2017	Shanghai, China	**Animal Toxicity Study**	88 male Sprague Dawley rats (6 to 8 weeks old)	Rats were treated with $PM_{2.5}$ via intratracheal instillation.	Randomly assigned to 11 different dosage treatment groups: Vit E groups, O3FA groups, and combined treatment (Vit E + O3FA) groups.	Cardiovascular health biomarkers include inflammatory cytokines (TNF-α, IL-1, IL-6) and oxidative stress (SOD, GSH-Px, and MDA).	Rats in either the Vit E or O3FA treatment groups showed significant mitigation of inflammatory biomarkers (TNF- α, IL-1, IL-6) and increased antioxidant activity in combined treatment groups.	Supplementation with Vit E and O3FA could protect against $PM_{2.5}$-induced injury, but the combination of both produced more significant protection effects than alone.	Nutrients were given by lavage, thus not representative of human supplementation. • The mechanisms linking the protective effects of Vit E and O3FA have not been clearly studied.

Table 1A. *Cont.*

Title	Authors / Publication Year	Country/ Place	Study Design	Population	Exposure	Comparison	Outcome	Results	Study Conclusions	Notes/Gaps
Mitigation of Particulate Matter-Induced Inflammation and Vasoactivity in Human Vascular Endothelial Cells by Omega-3 Polyunsaturated Fatty Acids	Sriram et al., 2018	Columbus, OH USA	**Cell Toxicity Study**	HUVECs	Cells were treated with 100 µg/mL of DEP over two periods: 24-hrs and 48-hrs.	4 different treatment groups: EPA, DHA, a mixture of DHA/EPA (oil formulation), and no treatment.	Endothelial function, including pro-inflammatory cytokines (IL- 6 and IL-8) and ET-1.	DHA treatment was effective in mitigating the levels of pro-inflammatory cytokines, while EPA seemed more successful at reducing ET-1 levels.	All O3FA-treated cell groups were effective at mitigating PM-induced endothelial effects.	The O3FA supplementation was not completely representative of the treatment in human subjects. • Even though the dosage of O3FAs were calculated according to human intake and absorption rates, it cannot completely represent human treatment.
Omega-3 Fatty Acid Prevents Heart Rate Variability Reductions Associated with Particulate Matter	Romieu et al., 2005	Mexico City, Mexico	**Human Exposure Panel Study** [Randomized, Double-Blinded, Placebo-Controlled]	50 adults (nursing home residents older than 60 years old)	Daily 24-hr measurements of ambient $PM_{2.5}$ indoors via Mini-Vol portal air samplers and outdoors via a fixed monitor on the roof.	Randomly assigned to either fish oil (2 g/day) or soy oil (2 g/day) as the control for the 5-month supplementation phase. A pre-supplementation phase occurred for 1 month.	Cardiac responses, including HRV.	Participants in the soy oil group had non-significant protection from the effects of $PM_{2.5}$ on HRV, whereas fish oil attenuated the effects of $PM_{2.5}$ exposure on HRV.	Supplementation with 2 g/d of fish oil protected against HRV decline related to $PM_{2.5}$ exposure.	Small sample size. • Short-term HRV recordings, which could lead to incorrect assessments of LF.
Dietary Supplementation with Olive Oil or Fish Oil and Vascular Effects of Concentrated Ambient Particulate Matter Exposure in Human Volunteers	Tong et al., 2015	Chapel Hill, NC USA	**Controlled Human Exposure Study** [Randomized, Double-blinded, exposure controlled]	42 adults (middle-aged, aged 50 to 72 years old)	Participants inhaled CAP via face mask in a controlled chamber (mean, 253 ± 16 ug/m^3) in 2-hr exposure periods. CAP was obtained by drawing ambient air from the roof and passing through a 2-stage aerosol Harvard concentrator, producing up to a 30-fold increase in particle number and mass.	Randomly assigned to either olive oil group (3 g/day) or fish oil group (3 g/day) or no supplements (naïve) for 4 wks prior to controlled exposure.	Endothelial function, including flow-mediated dilation and ET- 1, and inflammation.	Participants in the fish oil and naïve groups were observed to show endothelial dysfunction (measured by lower flow-mediated dilation) after exposure, but not in the olive oil group.	Instead of fish oil supplements, olive oil supplements attenuated the harmful effects on endothelial function after CAP exposure.	A standard crossover design involving randomized exposure to air and CAP was not used. • Conclusions derived from the small number of participants may not apply to the whole population. • The modest sample size and the number of measured secondary endpoints could inflate the findings' significance.
Increases in Ambient Particulate Matter Air Pollution, Acute Changes in Platelet Function, and Effect Modification by Aspirin and Omega-3 Fatty Acids: A Panel Study	Becerra et al., 2016	Rochester, NY USA	**Human Exposure Panel Study**	30 adults (Type II diabetes mellitus, aged 40 to 80 years old)	Hourly PM concentrations ($PM_{2.5}$, UFP, and BC) were measured from the fixed site at the Environmental Protection site in Rochester, NY.	8 weeks of therapy, with first a single dose of aspirin (81 mg/day) for 7 days, discontinued to follow up with a 28-day regimen of fish oil (4 g/day), followed by combined treatments of aspirin (81 mg/day) and fish oil (4 g/day).	Vascular effects, including increased platelet aggregation and thromboxane B2 production.	Combined treatment of aspirin and fish oil blunted the effect of PM on platelet function and thromboxane B2.	The effects of increased ambient PM on platelet function were lessened in subjects taking aspirin and/or fish oil (EPA and DHA). This is mainly since aspirin and EPA/DHA reduce pro-inflammatory and pro-thrombotic prostaglandins from arachidonic acid.	A small sample size (n=30) could have resulted in limited statistical power. • PM concentrations were collected by one site, not representing each study participant's exposure. • The participants' addresses were not geocoded.

Table 1A. *Cont.*

Title	Authors / Publication Year	Country/ Place	Study Design	Population	Exposure	Comparison	Outcome	Results	Study Conclusions	Notes/Gaps
Omega-3 Fatty Acid Supplementation Appears to Attenuate Particulate Air Pollution-Induced Cardiac Effects and Lipid Changes in Healthy Middle-Aged Adults	Tong et al., 2012	Chapel Hill, NC USA	**Controlled Human Exposure Study** [Randomized, Double-blinded, exposure controlled]	29 adults (middle-aged, 50 to 72 years of age)	Participants inhaled CAP via face mask in a controlled chamber (mean, 253 ± 16 ug/m^3) in 2-hr exposure periods. CAP was obtained by drawing ambient air from the roof and passing through a 2-stage aerosol Harvard concentrator, producing up to a 30-fold increase in particle number and mass.	Randomly assigned to either fish oil group (3 g/day) or olive oil (3 g/day) for 4 weeks before controlled exposure to CAP.	Cardiac responses, including HRV, cardiac repolarization, and blood lipid changes.	Fish oil attenuated CAP-induced reduction in HF/LF ratio and normalized LF-HRV. Participants in the olive oil group were not observed to have these same protective effects.	O3FA supplements offer protection against the adverse cardiac and lipid effects induced by PM exposure.	A standard crossover design involving randomized exposure to air and CAP was not used. • Conclusions derived from the small number of participants may not apply to the whole population. • The modest sample size and the number of measured secondary endpoints could inflate the findings' significance.
Omega-3 Supplementation Can Regulate Inflammatory States in Gas Station Workers: A Double-Blind Placebo-Controlled Clinical Trial	Barkhordari et al., 2020	Isfahan, Iran	**Human Clinical Trial** [Randomized, Double-Blinded, Placebo-Controlled]	53 adults (male, aged 45 to 58 years old)	Exposure to DPM, but not measured.	Randomly assigned to a fish oil group (3 g/day) or a placebo group.	Pro-inflammatory cytokines (IL- 12, IFN-γ, TNF-α, IL-10, and IL-17).	The concentrations of certain inflammatory cytokines (e.g., IFN-y and IL-17) were significantly decreased in the O3FA group compared to the placebo group. In contrast, the inhibitory biomarkers (or regulatory cytokines) of IL-10 and TFG-β were increased in the O3FA group.	O3FA supplementation significantly decreased the IL-17 and IFN-γ levels compared to the placebo group. The inhibitory cytokines IL-10 and TGF-β were increased in the O3FA group.	DPM exposure was not measured. • Placebo supplement is unknown.
Effect of Vitamin E and Omega-3 Fatty Acids on Protecting Ambient PM2.5-Induced Inflammatory Response and Oxidative Stress in Vascular Endothelial Cells	Bo et al., 2016	Shanghai, China	**Cell Toxicity Study**	HUVECs	Cells treated with 50 μg/mL of $PM_{2.5}$.	24 different dosage treatment groups: Blank groups, Vit E groups, O3FA groups, and combined treatment groups.	Endothelial function, including inflammatory cytokines (IL-6 and TNF-α), oxidative stress markers (SOD, MDA, and ROS), and cell viability (LDH).	Vit E reduced inflammatory cytokines and oxidative stress biomarkers, with similar results observed in high-dose O3FA groups. Combined treatment groups showed a significant reduction of inflammatory cytokines.	Supplementation with Vit E and O3FA could protect against PM2.5-induced damage in endothelial cells, but the combination of both produced more significant effects of protection than alone.	The O3FA and Vit E supplementation were not completely representative of the treatment in human subjects. • Even though the dosage of O3FA and Vit E were calculated according to human intake and absorption rates, it cannot completely represent human treatment.
PM2.5 Inhalation Induces Intracranial Atherosclerosis which may be Ameliorated by Omega-3 Fatty Acids	Guan et al., 2017	Beijing, China	**Animal Toxicity Study**	162 Sprague-Dawley rats (6 weeks old)	Rats were exposed to ambient $PM_{2.5}$ using a versatile aerosol concentration enrichment system in a controlled chamber.	Randomly divided into 3 groups: a normal chow diet, a high-cholesterol diet with O3FA supplementation (5 mg/kg/per day), or a high-cholesterol diet.	Vascular effects, including MCA morphology (measured by the thickness of the MCA and luminal diameter), systemic inflammation (TNF-α and IL-6), and vascular dysfunction biomarkers (VCAM-1 and iNOS).	O3FA supplementation significantly reduced the expression of TNF-α, IL-6, VCAM-1, and iNOS.	O3FA supplementation prevents ICA development and inflammatory reaction in cerebral vessels.	Nutrients were given by lavage, thus not representative of human supplementation.

Table 2A. List of Abbreviations

Abbreviations	
ALA	alpha-linolenic acid
A	autonomic nervous system
BC	black carbon
CAP	concentrated ambient particulate matter
COX	cyclooxygenase enzyme system
CRP	C-reactive protein
Cu/Zn	copper/zinc
DHA	docosahexaenoic acid
DPM	diesel particulate matter
ED	emergency department
EPA	eicosapentaenoic acid
GPR120	G protein-coupled receptor 120
GSH	glutathione reductase
GSH-Px	glutathione peroxidase
H_2O	water
H_2O_2	hydrogen peroxide
HF	high-frequency
HRV	heart rate variability
HUVECs	human umbilical vein endothelial cells
ICA	intracranial atherosclerosis
ICAM-1	intercellular adhesion molecule 1
IHD	ischemic heart disease
IL-1β	interleukin-1β
IL-6	interleukin 6
IL-8	interleukin 8
ISA	Integrated Science Assessment
Iκβ	Iκβ kinase

Abbreviations	
LF	low-frequency
LPO	lipid peroxidation
MDA	malondialdehyde
MI	myocardial infarction
Mn	manganese
NF-κβ	Nuclear factor kappa β
NO	nitric oxide
NO_2	nitrogen dioxide
O_{2-}	superoxide anion
O_3	ozone
O3FA	omega-3 fatty acid
PECO	population exposure comparison outcome
PM	particulate matter
PM_{10}	coarse particulate matter, >10 μm
$PM_{10-2.5}$	particulate matter, 2.5-10 μm
$PM_{2.5}$	fine particulate matter, <2.5 μm
PPAR-γ	peroxisome proliferator-activated receptor gamma
PRISMA	preferred reporting items for systematic reviews and meta-analyses
RNS	reactive nitrogen species
ROS	reactive oxygen species
SOD	superoxide dismutase
SPMs	pro-resolving mediators
TAC	increasing total antioxidant capacity
TNF-α	tumor necrosis factor α
UFP	ultrafine particle matter, <0.1 μm
VCAM-1	vascular cell adhesion protein 1
Vit E	vitamin E