Role of Omega 3 Fatty Acids in the Prevention and Treatment of Cardiovascular Disease

An Honors Program Thesis

by

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Need for the study:

Cardiovascular disease (CVD) has been the major cause of death every year in the United States since 1919 (Krummel, 2008), and it is also the leading cause of death globally (World Health Organization, [WHO], 2009). Most CVD related deaths occur in adults older than 65 years of age. However, one third of these deaths occur before the individual has reached the average life expectancy (Krummel, 2008). Cardiovascular disease includes the conditions of hypertension (HTN) and coronary heart disease (CHD), which both increase one’s risk of suffering a stroke (Krummel, 2008). Stroke is the third leading cause of death in this country (Centers for Disease Control and Prevention [CDC], 2010). Both HTN and CHD are prevalent in the United States. In 2006, the American Heart Association (AHA) estimated that over 17 million Americans had CHD and more than 425,000 Americans died from this disease that same year (AHA, 2010). The CDC estimated that one in three American adults has HTN (CDC, 2010). Cardiovascular disease is an expensive public health problem in this country, as related costs were estimated to exceed 403 billion dollars in 2006 (Krummel, 2008).

The causes of HTN and CHD are multifactorial and include both genetic and lifestyle factors. Current recommendations for individuals trying to prevent the development of these chronic conditions include: altering lifestyle choices by increasing activity level, quitting smoking, and consuming a healthier diet. However, a family history of HTN or CHD is a risk factor one cannot control. Despite the increase in national attention regarding prevention of these diseases, the United States ranks 13th for the prevalence of CVD in women and 17th in men among industrialized nations (Krummel, 2008).

Traditional treatment recommendations for CVD include a combination of lifestyle and dietary modifications, and drug therapies. Omega 3 fatty acids (Ω-3 FA) are a more cost
effective treatment option for CVD than traditional drug therapies. Consumption of Ω-3 FA is an additional, yet alternative option, which may reduce the risk of mortality from CHD and HTN for those already diagnosed and it may reduce the risk of developing these chronic diseases in undiagnosed adults. Despite the availability of traditional treatments, mortality from CVD remains a prevalent problem (Krummel, 2008).

**Problem Statement:**

The purpose of this review is to determine the degree to which consumption of dietary and supplemental sources of Ω-3 FA aids in the prevention and treatment of CVD in adults.

**Subproblems:**

1. What are the effects of Ω-3 FA in the prevention of CVD in adults?
2. What are the effects of Ω-3 FA in the treatment of CVD in adults?

**Hypothesis:**

1. Adults previously diagnosed with HTN or CHD who consume either dietary or supplemental sources of Ω-3 FA will have lower rates of mortality from CVD related causes than adults who do not consume Ω-3 FA.
2. Adults who have not been diagnosed with HTN or CHD and who consume either dietary or supplemental sources of Ω-3 FA will have a reduced risk of developing HTN and CHD and lower rates of mortality from CVD related causes than adults who do not consume Ω-3 FA.
**Definition of terms:**

Adults: People ages 18 to 50.

Cardiovascular Disease: For the purpose of this paper, CVD is defined as a diagnosis of CHD or HTN by a physician. Diagnosis of HTN will be confirmed with evidence of systolic blood pressure (SBP) greater than or equal to 140 mmHg and diastolic blood pressure (DBP) greater than or equal to 90 mmHg. Diagnosis of CHD will be confirmed by the research study physician’s analysis of electrocardiogram or electron-beam computed tomography test results, or by evidence of prior myocardial infarction (MI).

**Delimitations:**

1. The participants diagnosed with CVD before the start of the study are limited to those diagnosed with either CHD or HTN.

2. Adults diagnosed with both CHD and HTN simultaneously will be excluded.

3. Adults not diagnosed with HTN or CHD are limited to those without a first degree relative diagnosed with CVD or who died from CVD related causes.

**Methods and Materials:**

Reference materials were obtained through searches using the online databases at the C.W. Post Campus of Long Island University. The electronic databases Medline-Ebsco, the *Journal of the American Heart Association*, the *Journal of the American Medical Association*, the *European Journal of Clinical Nutrition*, the *New England Journal of Medicine*, *The American Journal of Clinical Nutrition*, the *European Journal of Nutrition* and the *Journal of Nutrition* were used to search for research articles pertaining to this topic. Of the 1,638 total articles found, only 18
were used in this paper. The following search terms were used to find the electronic journal articles:

- Omega 3 fatty acids and cardiovascular disease
- Dietary omega 3 fatty acids and prevention of heart disease
- Omega 3 fatty acids and heart disease
- Omega 3 fatty acids, blood pressure (BP), HTN
- Omega 3 fatty acids and heart disease
- Fatty fish and coronary heart disease
- Flaxseed and cardiovascular
- Omega 3 or flax or fish and blood pressure
- Fish consumption and heart

**Review of Literature:**

**Introduction**

Since the 1900s, CVD has been the major cause of death every year in the United States, excluding 1918 (Krummel, 2008). Additionally, CVD is the leading cause of death globally (WHO, 2009). This is a major public health problem in this country, as related costs were estimated to exceed 403 billion dollars in 2006 (Krummel, 2008). The majority of CVD fatalities occur in adults older than 65 years of age. However, one third of deaths related to CVD occur before one has reached the average life expectancy (Krummel, 2008).

Cardiovascular disease is a broad term that includes many conditions such as CHD, cerebrovascular disease, peripheral artery disease, rheumatic heart disease, congenital heart disease, and HTN (WHO, 2009). This literature review will focus on CHD and HTN.
According to the CDC (2010), having high BP or HTN raises a person’s risk for developing heart disease and stroke, which are the first and third causes of death in this country.

Since CVD is a prevalent problem, Healthy People 2020, the ten year national objective “…for promoting health and preventing disease” has created objectives to address this problem. (Healthy People, 2010). The overarching goals of Healthy People 2020 are to increase the number of healthy years in one’s life and to eliminate health disparities. Many objectives included in Healthy People 2020 relate to promoting cardiovascular health and preventing related diseases. Reducing mortality from heart disease, increasing the number of individuals whose high BP is controlled, and increasing the number of people who had their BP measured within the past two years and understanding if it is normal or elevated, are some of the goals of Healthy People 2020. Other goals of Healthy People 2020 are to reduce the number of people with HTN and to increase cardiovascular health overall in the United States. For those already diagnosed with HTN, Healthy People 2020 aims to increase the number of Americans meeting recommended guidelines for body mass index (BMI), saturated fat and sodium consumption, physical activity, and moderate alcohol consumption (Healthy People, 2010).

Although mortality rates are high for people diagnosed with CVD, there are medications, medical nutrition therapies, and lifestyle factors that can help reduce a person’s risk of developing or dying from the disease (Krummel, 2008). For many CVDs, recommendations include: stop smoking cigarettes, adopt a more active lifestyle, and consume a healthier diet (CDC, 2010). Medical nutrition therapies include lowering saturated fat to less than 7% of total calories and total fat intake to 25 and 35% of total calories. Consuming plant stanols, soy, and fiber are other dietary recommendations. The Dietary Approaches to Stop Hypertension (DASH) Diet, which emphasizes consumption of whole grains, legumes, and lean fish, meat, and poultry,
is an appropriate therapy for treating CVD. In addition to these traditional recommendations, use of alternative therapies has gained national attention. One alternative therapy currently being researched is consumption of omega 3 fatty acids (Ω-3 FA). The current recommendation for Ω-3 FA for adults without CHD is to eat fatty fish two times per week (Ismail, 2007). For patients diagnosed with CHD, they are encouraged to consume one gram (g) per day of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) or two to four g per day from supplements, if under the care of a physician (Ismail, 2007).

This literature review will examine the research on the potential role of Ω-3 FA in the prevention and treatment of CVDs, such as CHD and HTN. It will also include existing literature on consumption of dietary versus supplemental sources of Ω-3 FA.

Cardiovascular Disease

Incidence and prevalence

In 2006, it was estimated that over 81 million Americans had one or more forms of CVD (American Heart Association [AHA], 2010). The United States ranks 13th for the prevalence of CVD in women and 17th in men among industrialized nations (Krummel, 2008). In addition, it was reported that more than 831,000 people died of CVD in 2006.

Types of Cardiovascular Disease (CVD)

Cardiovascular disease includes conditions such as HTN, CHD, stroke, heart failure, congenital heart disease, cerebrovascular disease, peripheral artery disease and rheumatic heart disease (WHO, 2009). This literature review will focus on HTN and CHD. Each of these conditions has specific causes, risk factors, and traditionally recommended treatments.
Coronary Heart Disease (CHD)

Coronary heart disease is a condition that is characterized by impaired blood flow in the arteries of the heart, which can result in death (Krummel, 2008). The AHA estimated that in 2006, over 17 million Americans had CHD and over 425,000 Americans died from this disease that year (AHA, 2010).

The most common cause of CHD is atherosclerosis, which is the accumulation of plaque in the arteries (Krummel, 2008). As plaque accumulates, ischemia can occur because of insufficient blood flow due to increased oxygen demand or due to constriction or obstruction of a blood vessel. Coronary heart disease is often referred to as a silent disease because many people do not show any symptoms until they suffer a MI, also referred to as a heart attack. Arterial changes start in infancy and continue into adulthood asymptotically if a person has risk factors, such as family history of CHD. Coronary heart disease occurs when blood flow in the coronary arteries is impaired, which results in angina, MI, and sudden death. Myocardial infarctions are often fatal (Krummel, 2008).

The AHA has identified seven risk factors that contribute to the development of CHD (Krummel, 2008). Tobacco use, specifically cigarette smoking, has been found to directly influence acute coronary events. Physical inactivity may increase the risk for CHD at the same rate as elevated blood cholesterol, HTN, or tobacco use. Poor diet, especially consuming large amounts of excess calories, increases obesity rates and risk of CHD. A high fat, especially high saturated fat, diet increases risk. Lastly, a family history of CHD is a strong non-modifiable risk factor (Krummel, 2008).

The Framingham Heart Study has identified additional CVD risk factors (Krummel, 2008). This study began in Framingham, Massachusetts in 1948. With an initial sample
population of 5,209 people, the Framingham Heart Study is the largest epidemiological study of CVD worldwide to date. The initial participants were healthy adults ages 30 to 62 years. This study has continued by examining the children and grandchildren of the initial cohort. The concept of CVD risk factors and prevention began with this study. The seven major risk factors for CVD were age, gender, BP, total cholesterol (TC), high density lipoprotein (HDL) cholesterol, smoking, glucose intolerance, and left-ventricular hypertrophy. Other major findings from the Framingham Heart Studies included that obesity was associated with increased risk of CVD, menopause increased the risk of CVD, and that psychosocial factors affect heart disease. The Adult Treatment Panel III is based on the findings of the Framingham Heart Health Study (Krummel, 2008). This tool is used to determine the ten year risk for women and men who do not have CVD or type 2 diabetes mellitus (DM) for the development of CHD and stroke. Risk estimates are based on the determined CVD risk factors and include lower risk, moderate risk, moderately high risk, high risk, and very high risk. Each risk level has a recommended low density lipoprotein (LDL) cholesterol target level. Those with the lowest risk level for CVD should aim to achieve a target LDL of <160 mg/dl, and those with the highest risk level have a target LDL of <70 mg/dl (Krummel, 2008).

Role of omega 3 Fatty Acids in Prevention of CHD

Recent and currently emerging evidence from studies indicates a relationship between consumption of Ω-3 FA and reduced risk of developing CHD. Omega 3 FAs are essential because they cannot be synthesized by the human body, and must be consumed through dietary or supplemental sources to prevent a deficiency (Watkins & Hutchins, 2010). These FAs are polyunsaturated, which contain two or more double bonds (Omega 3 learning). Omega 3 FAs
are naturally present in a variety of dietary sources, including canola oil, walnuts, soybeans, marine cold water fish, fish oil, flaxseed oil, and flaxseed. Some egg and milk products are now fortified with \( \Omega-3 \) FA. The different types of \( \Omega-3 \) FA include alpha-linolenic acid (ALA), which is the form present in vegetarian sources. Alpha-linolenic acid is unique because it has to be converted to the more active forms of \( \Omega-3 \) FA, which are EPA and DHA. However, the conversion of ALA to EPA is a partial one, and is estimated to be only 8% in men and 21% in women (Watkins & Hutchins, 2010). Since this conversion is not complete, many experts recommend that people consume \( \Omega-3 \) FA from dietary fish sources, foods fortified with EPA or DHA, or reputable supplements containing EPA and DHA.

Omega 3 FA and omega 6 FA (\( \Omega-6 \) FA) have opposing functions in the body (umm.edu). Although \( \Omega-6 \) FAs are essential for normal body function, many Americans consume them in excess amounts compared to \( \Omega-3 \) FA (Watkins and Hutchins, 2010). The recommended ratio of consumption for \( \Omega-6 \) to \( \Omega-3 \) FA is 2.3 to 1. The typical American diet is estimated to contain 14 to 25 times more omega-6 FA than omega-3 FA (umm.edu). Omega 3 FAs act to reduce inflammation, while \( \Omega-6 \) FA tends to promote inflammation. It is recommended to balance consumption of \( \Omega-3 \) FA and \( \Omega-6 \) FA for this reason.

Studies have been conducted on the effectiveness of \( \Omega-3 \) FA in preventing the development of CHD. In a randomized, double blind intervention trial, the effects of consumption of marine sources of \( \Omega-3 \) FA and industrially manufactured trans fatty acids on cardiac risk factors in healthy males were compared (Dyerberg et al., 2004). Eighty-seven male participants between 20 and 60 years of age, with normal echocardiogram (ECG) and BP, and no abnormal biochemical test results were included in this study. Participants were randomly divided into three groups: controlled fat diet, a trans fatty acid (TFA) enriched diet, and a \( \Omega-3 \)
FA polyunsaturated fat (PUFA) enriched diet. Each group followed a particular diet for eight weeks. The participants received instruction on how to follow the assigned diet and how to keep a weighted food journal three times throughout the duration of the trial. All tests conducted to determine outcomes of the treatment were performed after at least ten hours of fasting, seven times throughout the trial (Dyerberg et al., 2004).

Results showed that a minor decrease in arterial BP was observed for the participants in the PUFA group, which was significantly different from the control group \((p < .05)\) (Dyerberg et al., 2004). The mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) for the PUFA group at baseline was 131.7 mmHg and 80.9 mmHg, respectively. In addition, a decrease in triglyceride (TG) concentration was observed for those in the PUFA group from 1.34 to 0.99 mmol/L. After eight weeks, mean SBP and DBP for the PUFA group decreased to 127.6 and 76.8 mmHg, respectively. A decrease in HDL-cholesterol levels for the TFA group from 1.32 mmol/L at baseline to 1.26 mmol/L after eight weeks was observed \((p < 0.05)\). Overall, no effect on heart rate variability or endothelial function was observed for any of the groups. In conclusion, the researchers were not able to confirm the effects of consumption of marine sources of \(\Omega-3\) FA on endothelial function. However, this could be attributed to the healthy state of the participants in this trial or to the use of food sources of \(\Omega-3\) FA rather than supplemental forms used in other trials (Dyerberg et al., 2004).

Another study aimed to determine an association between high intakes of fish and \(\Omega-3\) FA and reduced risk of mortality from heart disease (Yamagashi et al., 2008). This study was a large scale, nationwide prospective study. It was estimated that fish consumption in Japan was at least three or four times greater than in the United States. Potential participants completed questionnaires indicating their lifestyle choices and previous medical histories of CVD or cancer;
those who were diagnosed with either of these conditions before baseline were not included in the study. The final participants included 22,881 men and 35,091 women ages 40 to 79 years during the baseline period. Subjects completed a food frequency questionnaire (FFQ) indicating how many times per week or month they consumed fish and other foods. Serving sizes were estimated based on a prior validation study, which also was utilized for determining the nutrient and fatty acid content of the foods. In order to determine whether an association existed, investigators performed systematic reviews of death certificates of the participants, since registration of death is required by law in Japan. The mean period of follow-up was 12.7 years. Quintiles of fish intake and Ω-3 FA intake were used to determine data for mortality rates. Covariates included BMI, whether and/or how frequently and for how many years the participant smoked cigarettes, past medical history of HTN and DM, and frequency of alcohol intake. During the follow-up period, 419 deaths were attributed to ischemic heart disease, 107 from cardiac arrest, and 307 from heart failure. In total, 7,008 participants died. Of these deaths, 2,045 were attributed to total cardiovascular diseases. Researchers concluded that fish and Ω-3 FA intake were inversely associated with risk of mortality from heart failure and total CVD. The multivariate hazard ratio (95% CI) for the highest quintiles of fish versus the lowest for development of total CVD was 0.83 (0.68 to 1.02) for women and 0.84 (0.69 to 1.04) for men (p < .001 for this trend in both men and women). Dietary consumption of fish and Ω-3 FA in the highest quintile was associated with 18 to 19% lower death risk from total CVD compared to the lowest quintile (Yamagashi et al., 2008).

Data collected from the Nurses’ Health Study was used to determine the association between fish and Ω-3 FA consumption and risk of developing CHD in women (Hu et al., 2002). The participants included 84,688 nurses who were 34 to 59 years old at baseline in 1980.
Potential participants who had a previous medical history of cancer, MI, stroke or other CVDs before baseline were excluded. Dietary data were compared from validated questionnaires that were completed by participants in 1980, 1984, 1986, 1990, and 1994. Participants completed a FFQ indicating how often during the previous year they consumed a standard amount of a particular food, such as fish, in order to estimate Ω-3 FA and fish intake (Hu et al., 2002).

Throughout the 16 years of follow-up, 1,513 participants were diagnosed with CHD. Of these participants, 484 died and 1,029 suffered a nonfatal MI (Hu et al., 2002). In total, 4,121 deaths attributed to all causes were reported. Fish and Ω-3 FA consumption were associated with decreased risk of mortality from all causes. The determined multivariate relative risk (RR) for mortality from all causes was 0.68 (95% CI, 0.57 to 0.82), with a p value < .001 for women consuming fish at a minimum of five times per week compared to those who ate fish less than one time per month. Participants’ whose regular consumption of high amounts of foods containing Ω-3 FA were associated with a lower risk of developing CHD (Relative Risk [RR] = 0.62; 95% CI, 0.41 to 0.92, p value for trend < .001). However, women who regularly consumed larger amounts of Ω-3 FA had a healthier diet and lifestyle than those who rarely consumed Ω-3 FA. Adjustment for these factors did not significantly alter the results, which suggests that fish and Ω-3 FA consumption may have an independent effect on risk of CVD. The inverse association between fish and Ω-3 FA intake and death from CHD was somewhat stronger (RR = 0.55 for fatal CHD; 95% CI, 0.33 to 0.90 and RR = 0.73 for nonfatal MI; 95% CI, 0.51 to 1.04) (Hu et al., 2002).

Researchers of a Dutch population based cohort study determined associations between fish, EPA, and DHA intake and risks of CHD and MI (Goede, Geleijnse, Boer, Kromhout, & Verchuren, 2010). The Monitoring Project on Risk Factors for Chronic Diseases study was a
cohort study of 22,654 men and women, ages 20 to 65 years old. Information on diet, lifestyle, and CVD risk factors were collected from participants from 1993 to 1997. For this study, random samples that were stratified by gender and five year age groups were drawn from three geographical areas of the Netherlands. The average response rate was 45%. Participants who did not provide consent for follow up (n=701), those without dietary information (n=72), and those with extreme intakes of energy (n=97) were excluded from the analysis. Those with a history of MI or stroke at baseline based on self-reports were excluded. The final analysis included 21,342 participants. Participants’ dietary intakes were assessed by a self-administered FFQ. They reported usual frequency of consumption of each item per day, week, month, year, or never, and the average serving sizes. Habitual fish intake was assessed in terms of lean and moderately fatty fish, fatty fish, and shrimp or mussels. The relative validity of the FFQ was assessed by 12 monthly 24 hour recalls. Reproducibility was measured by two repeated measurements of the FFQ. Validity and reproducibility were assessed among 121 participants. The Spearman rank coefficients for reproducibility were 0.49 and 0.61 for men and women, respectively. The rank coefficients for relative validity were 0.32 for men and 0.37 for women ($p < .05$). The participants were followed for occurrence of fatal CHD, fatal MI, and nonfatal MI through linkage with registries. They were followed until death, emigration, or January 2006 or 2007, or whichever occurred first. Trained research nurses at municipal health service sites collected information on body weight, height, and BP. Participants completed self-administered questionnaires concerning DM, history of MI and stroke, medications, vitamin or mineral supplement use, family history of MI, education level, alcohol consumption and cigarette smoking. Nonfasting blood samples were collected (Goede et al., 2010).
Participants were 42.1 ± 11 years old at baseline (Goede et al., 2010). Forty-five percent of participants were men. The median estimated intake of EPA and DHA and fish were 114 (62 to 195) mg/day and 7.4 (3.3 to 14.0) g/day, respectively. More than 8% of participants reported consuming no fish, and almost 40% consumed fish less than one time per month. The median consumption of fish was two times per month. Consumption of lean and moderately fatty fish (which were combined in the questionnaire) was three to four times as much as fatty fish. The mean follow up was 11.3 years, but the range was 9 to 14 years.

During follow up, 647 participants died (3%) (Goede et al., 2010). Eighty-two of these deaths were attributed to CHD (including 64 cases of MI). Two hundred fifty-two participants suffered a MI and survived. The participants in the higher quartiles of fish consumption tended to be slightly older, were more likely to be men, and were more educated. Those who consumed higher amounts of EPA and DHA were associated with a higher consumption of total energy and alcohol. The Spearman coefficient for total EPA and DHA consumption and fish consumption was 0.95. After adjustment for confounding variables, the risk of fatal CHD was inversely associated with EPA and DHA consumption. Those in the highest quartile for EPA and DHA (250 mg/day) had a 49% lower risk for fatal CHD than participants in the reference group (40 mg/day). A stronger association was observed between fatal MI and EPA and DHA consumption, as those in the highest quartile had a 62% lower risk. A dose-dependent relation was observed for fatal CHD ($p = .05$) and fatal MI ($p = .01$), while EPA and DHA consumption was not associated with nonfatal MI. Higher consumption of fish was associated with reduced risk for fatal CHD and fatal MI (Goede et al., 2010).

Another study found associations between consumption of fish and reduced risk of CVD (Streppel, Ocké, Boshuizen, Kok, & Kromhout, 2008). The Zupten Study started in 1960 with
middle aged men living in Zupten, Netherlands. A random sample was obtained from 1,088 men who lived in Zupten for a minimum of five years, and who were born between 1900 and 1919. Eight hundred and seventy-eight men were interested in participating (81%), but only 872 completed dietary and physical examinations. These exams were performed again in 1965 and 1970. In 1985, a new random sample of men was added to the study. The 554 men who were part of the original study population and who were still living continued to participate. Of the 1,266 new men invited to participate, 939 consented (74%). Eight hundred and twenty-five of these men completed the dietary and physical examinations, which were repeated in 1990, 1995, and 2000. A cross check dietary method was used to verify dietary information collected from the participants. Experienced dietitians interviewed participants on their dietary habits six months to one year prior. The average food consumption during a day or week, and quantity of foods purchased was estimated based on the information provided during the dietary interview and presented to the participants for them to verify if it was accurate. Total fish consumption was assessed in terms of fatty fish (salmon, mackerel, herring, eel, sardines), and lean fish (codfish, plaice, Pollack). Daily intake of EPA and DHA was estimated based on amount and type of fish consumed. Researchers calculated cumulative fish, EPA, and DHA intake to better represent long term consumption. Participants were divided into consumers and nonconsumers of fish according to their cumulative average of consumption. Blood pressure, weight, height, and BMI were assessed at the physical examinations. Information on DM and prevalence of other chronic diseases was collected and verified by contacting the participants’ primary care doctors. Socioeconomic status was assessed and it was used to classify participants into one of four categories. Participants were followed until death, or until the end of the study on June 30, 2000. A clinical epidemiologist ascertained the final causes of death. In the analysis,
researchers included both primary and secondary causes of death, because the ultimate cause of death can be more difficult to establish in older individuals (Streppel et al., 2008).

Confounding variables included total energy intake in kilocalories per day, alcohol intake, wine use, fruit and vegetable intake, saturated and trans fat consumption, use of a cholesterol lowering diet, smoking, SBP, socioeconomic status, and prevalence of DM (Streppel et al., 2008). Of the 1,373 men participating in the study, 348 died from CHD during the 40 years of follow up. Sixty-six of these deaths were sudden coronary deaths (19% of total CHD deaths). Mean age of death was 77 years. Of the men who started the study in 1960, between 71 and 81% consumed fish between 1960 and 2000. The average fish consumption was 16 to 21 g per day. Average intake of EPA and DHA was estimated to be between 136 and 236 mg per day. Consumption of EPA and DHA was comparable for the men who started participating in the study in 1985. The cumulative average for fish consumers was 22 g per day. These participants had a 27% lower risk of death from CHD than nonconsumers of fish. Researchers observed a significant and positive interaction with age for the association between long term fish intake or EPA and DHA intake with CHD death ($p = .06$). These associations were weaker at older ages. The HR for long term fish consumption was 0.32 (95% CI, 0.13 to 0.80) at age 50, and 0.65 at age 65 (95% CI, 0.42 to 1.02), compared to no fish consumption. The confidence intervals were too wide after age 70 for researchers to draw conclusions. Researchers observed an inverse association between EPA and DHA consumption and death from CHD, for those participants who consumed below and above 250 mg per day compared to those who did not consume fish daily. The association between fish consumption and death from CHD was strengthened after adjustment for MI, stroke, and cancer. Long term fatty fish consumption, which was on average, 7 g per day, reduced the risk of sudden death from CHD by 54% (95%
CI, 0.27 to 0.74. This inverse association was independent of total fish consumption (Hazards Ratio [HR] = 0.41, 95% CI, 0.23 to 0.73). No clear dose-response relationship was found, despite the finding that the association between EPA and DHA intake from fish and EPA and DHA was stronger for men who consumed more than 250 mg per day than those who consumed less than this amount. Researchers concluded that long term fish consumption, in this case an average of 22 g per day or one to two servings per week, was inversely associated with death from CHD. As age increased, the strength of this association decreased. However, this association was statistically significant up until age 65 (p = 0.06). Long term fatty fish consumption was associated with reduced risk of death from CHD independent of age (Streppel et al., 2008).

A large scale prospective cohort study aimed to determine the association between intake of marine Ω-3 FAs, fish intake, and the risk of CVD in men (Asherio, Rimm, Meir, Stampfer, Giovannucci, & Willett, 1995). The Health Professionals Follow-up Study started in 1986, and included 51,529 male health professionals who were not diagnosed with CVD. The participants completed detailed FFQs and provided information about their medical histories, risk factors for CVD, and dietary changes during the previous ten years. The FFQs included questions concerning fish intake; the FFQ administered in 1988 included a question about use of a fish oil supplement. The validity of the FFQ was assessed in a random sample by comparing calculated intake of Ω-3 FA from fish to Ω-3 FA levels in adipose tissue. The mean fish intake was determined to be 3.6 servings per week. Follow up questionnaires were given to participants in 1988, 1990, and 1992. Some of these participants were excluded from continuing their participation due to diagnosis of MI, angina, stroke, ischemic attack, or peripheral artery disease. The 44,895 eligible participants were followed for six years for occurrence of CHD. Participants
had follow-ups every two years, which was complete for 94% of participants. Those who did not respond to follow-up were assumed to be alive if they were not on the National Death Index. Participants who reported surviving a MI, coronary-artery bypass surgery, or angioplasty were asked for permission to review their medical records. Nonfatal MI was confirmed if it met the WHO criteria (Asherio et al., 1995).

The participants were divided into six groups based on fish intake as indicated on the FFQs (Asherio et al., 1995). Mean fish consumption was 1.2 and 5.8 servings per week for participants in the lowest and highest groups of fish intake, respectively. During the six years of follow-up, 1,543 cases of coronary events were reported, 547 of which were nonfatal MIs, and 732 were coronary-artery bypass or angioplasty procedures. Consumption of ω-3 FA from fish was directly associated with overall risk of coronary events in age-adjusted analysis (RR = 1.19 for men with highest intake compared to lowest, 95% CI, 1.02 to 1.39, \( p = .03 \)). Men with a higher intake of ω-3 FA from fish had an increased frequency of bypass grafting. However, researchers attributed this finding to the possibility that men who had higher fish intakes may have been more health conscious and willing to have angioplasty or elective coronary surgery. The risk of sudden death was not inversely associated with consumption of ω-3 FA. Researchers observed the highest risk for fatal CHD among men who did not consume fish; however, the risk did not decrease with increasing fish consumption (RR = 0.74; 95% CI, 0.44 to 1.23 for men who ate any fish compared to those who ate no fish). Use of fish oil supplements was not significantly associated with risk of CHD. The RR for users of fish oil was 0.96 (0.68 to 1.35) compared to nonusers of fish oil. No significant inverse association between fish or fish oil consumption and risk of MI was determined. The researchers concluded that there was no evidence of an association between marine ω-3 FA or fish consumption and risk of CHD. The
results of this study suggest that increasing fish consumption from one to two, or from five to six servings per week, in men who are not diagnosed with CHD, would not significantly reduce the risk of developing CHD (Asherio et al., 1995).

The purpose of a recent study by Barceló-Coblijn et al. (2008) was to determine whether consumption of flax or fish oil would provide greater cardiovascular benefits. Firefighters in a particular geographic area were contacted to participate because as a profession they are exposed to risk factors of CHD, including high stress levels, high fat intake, and limited physical activity. Potential participants diagnosed with DM, those taking lipid-lowering medications, or consuming supplements of any kind were excluded. The 62 selected participants were assigned by use of random number tables to one of six treatment groups. These groups were the 1.2, 2.4, and 3.6 g of flax seed oil per day in capsule form, 0.6 and 1.2 g of fish oil capsules per day, and the control group, which consumed two placebo pills (1 g of sunflower oil per capsule). The capsule stage of the study lasted 12 weeks. Participants’ BP, anthropometric data, three day dietary intakes, BMI, weight, and medical histories were assessed by trained personnel. Blood work was collected before the trial started and every two weeks during the trial. Plasma lipid profile, consisting of TC, TG, and HDL were determined for each participant (Barceló-Coblijn et al., 2008).

Results indicated that the ALA blood concentrations in the 3.6 g of flax oil per day increased significantly compared to the control group until week eight of the study (Barceló-Coblijn et al., 2008). After the eighth week, ALA content slightly decreased in this group, which may represent the conversion of ALA to EPA and then to DHA. The ALA concentrations also increased in the 2.4 g of flax oil group and became significant after the fourth week of treatment; however, the ALA content was not significantly affected in the fish oil groups. The DHA
content increased only in the fish oil groups, which may indicate that the conversion of ALA to DHA, and incorporation into red blood cells (RBC) was low during this study for the flax oil groups. No significant changes between the groups were determined with respect to TC, TG, or HDL. The dosages used in this study associated with changes in blood work tended to have maximum effects after six to eight weeks of treatment. The researchers concluded that consumption of 2.4 g of flax oil per day was sufficient to increase RBC phospholipid Ω-3 FA (Barceló-Coblijn et al., 2008).

Another recent study focused on the effectiveness of flaxseed consumption on reducing risk factors for cardiovascular disease (Bloedon et al., 2008). The participants were 62 men and post-menopausal women ages 44 to 75 years (31 men and 31 women). They were all hypercholesterolemic, as defined by having a pre-study fasting LDL of 130 to 200 m/dL and a fasting TG level of less than 600 mg/dL. People diagnosed with CVD, DM, or those who used any dietary supplements other than multivitamins, calcium, or vitamin D, hormone replacement therapy, or lipid lowering medications were excluded. Eligible participants were seen by a Registered Dietitian and instructed to follow a low-fat, low cholesterol diet that provided less than 30% of total calories from fat, less than 10% of calories from saturated fat, and less than 300 mg of cholesterol per day until the end of the study. After four weeks of following the prescribed diet, participants completed a questionnaire, which was used to determine their adherence. Those who met the minimum score on the questionnaire were randomized in a 1 to 1 ratio to the flaxseed group or the control group. This study was double-blind. Twenty grams of ground yellow omega flaxseed or wheat bran was baked into one of three breads or muffins. The participants in the flaxseed group received the flaxseed enriched products and those in the control group received the wheat bran containing products. They were instructed to consume
one test product in the morning and one at night every day for ten weeks. These products were
taste tested prior to the start of the study, and were similar in appearance. Fasting blood samples
were collected at the beginning of the study, week five, and at week ten. Compliance with
consuming test products was determined by self-reported diaries. Three day food records,
including two weekdays and one weekend day, were used to determine adherence to the low-fat,
low cholesterol diet (Bloedon et al., 2008).

The primary endpoint was the percent change in LDL from the start of the study to the
end (Bloedon et al, 2008). Percent change in TC, HDL, and very low density lipoprotein
(VLDL) cholesterol were secondary endpoints. Fifty eight of the enrolled participants (94%)
completed all visits related to the study. There were no differences in baseline characteristics
between the flaxseed and control group (p < .05). Results indicated that flaxseed consumption
significantly increased plasma levels of Ω-3 FA, ALA (p < .001), and docosapentaenoic acid
DPA (p < .001) compared to the wheat bran consumption. Participants in the flaxseed group had
reduced levels of the Ω-6 FA arachadonic acid at week ten compared to those in the control
group. This reduced the ratio of Ω-6 to Ω-3 FA. Mean adherence was determined to be 96% ±
11% at week five, and 92% ± 18% at week ten. By week ten of the study, 90% of participants in
the flaxseed group and 77% of those in the control group believed they were consuming
flaxseed-enriched products. No significant change in glucose, insulin or high sensitivity-C
reactive protein (hs-CRP) levels in either group at week five or at week ten was observed.
Flaxseed was also determined to not affect serum oxidized LDL levels. Forty-one subjects
experienced a total of 40 adverse effects (AE) during the study. Thirteen of these AE were
gastrointestinal related in the flaxseed group and eight in the control group. This study is the
second largest flaxseed trial to date for any condition. Despite the occurrence of AE, researchers
reported that including 40 g of ground flaxseed through baked products daily was well tolerated, and affected several factors of CVD risk. Consuming 40 g of ground flaxseed per day in addition to following a low-fat, low cholesterol diet, reduced LDL levels at week five; however, these changes were not significant at week ten. This decrease in efficacy may be explained by a reduction in adherence to the intervention and diet, or to biological adaptation. This result is in agreement with other related trials, in which flaxseed consumption up to six weeks had a significant LDL reducing effect, but studies that lasted longer than ten weeks did not report reductions in LDL levels. Researchers concluded that flaxseed consumption significantly lowered HDL levels in men, but not women (Bloedon et al., 2008).

Another study aimed to compare the effects of consumption of fish and fish-oil supplements on the Ω-3 FA content of RBCs and plasma phospholipids (PPLs) (Harris, Pottala, Sands & Jones, 2007). Few previous studies have addressed differences in bioavailability of Ω-3 FA from fish or fish oil supplements. Premenopausal women ages 21 to 49 years old at the start of the study were contacted to participate. Those who were pregnant, nursing, had a BMI greater than 30 kg/m², intended to lose weight, consumed more than two alcoholic drinks per day, consumed tuna or salmon more than two times per month, or consumed fish oil or flaxseed oil supplements were excluded. The 23 women selected to participate were randomly assigned to the fish or the fish capsule group. Eleven women were in the fish group and 12 were in the fish capsule group. Those in the fish group were instructed to consume three six-ounce cans of tuna and one 171 g filet of salmon every two weeks. Women in the fish capsule group were instructed to take 17 capsules over a two week period, or one to two capsules per day. The particular capsule selected by researchers was chosen because the FA composition more closely reflected that of salmon, as it was richer in DHA than EPA. Researchers estimated that three
cans of albacore tuna and one fillet of salmon provided 1,333 mg of EPA and DHA per week, or 485 mg per day. Seventeen fish oil capsules were estimated to provide 482 mg of EPA and DHA per day over a two week period (Harris et al., 2007).

The duration of this study was 16 weeks (Harris et al., 2007). Tolerability of the treatments was assessed by a questionnaire. Participants had visits at the clinic every two weeks, at which time the participants’ blood samples were drawn after a minimum ten hour fast. The fish and fish capsule groups did not differ significantly in terms of BMI; however, they did differ significantly in terms of age (35 ± 8.7 and 43 ± 8 years, respectively). There was no observed significant weight change during the study in either of the groups. Researchers determined that regardless of the source of Ω-3 FA, after 16 weeks of treatment there was no difference in the effect on Ω-3 or Ω-6 FA in RBCs or PPL. Consumption in both groups was associated with a 40 to 50% rise in RBC EPA and DHA, and a 60 to 80% rise in PPL EPA and DHA levels. Researchers found that EPA and DHA concentrations increased more quickly in PPL than in RBCs. This result confirms previous findings that turnover of EPA and DHA in plasma occurs more quickly than in RBCs. After the first month of treatment, the concentrations of EPA in RBCs did not differ significantly between the groups. This may indicate that EPA may be more bioavailable in fish than in fish capsules in the short-term. Completed questionnaires from participants indicated that fish consumption was associated with fewer complaints of an aftertaste, and had higher tolerability than the fish capsules. The duration of this study was 16 weeks because researchers determined that the lifespan of RBCs is 16 weeks, and they wanted the study to be long enough to achieve a steady state in both Ω-3 FA markers. However, this did not occur as the EPA and DHA content was still increasing at week 16. Various doses of Ω-3 FA were not used in this study. Researchers suggest that future studies on this topic should
include men and women, a larger variety of ages, and should last for more than four months. They concluded that EPA and DHA content of RBCs and PPLs did not differ significantly when equivalent doses of Ω-3 FA from fish and fish oil capsules were consumed. These results suggest that either source could be used to increase tissue Ω-3 FA concentrations (Harris et al., 2007).

In a recent study, researchers assessed the effects of fish oil consumption in addition to high or low intakes of linoleic acid (LA) on risk factors for CVD (Damsgaard, Frøkiær, Anderson, & Lauritzen, 2008). A randomized, double blind study that included 66 healthy male participants, ages 19 to 40 years was conducted. Healthy men with no chronic diseases, no regular use of medications, who smoked less than five cigarettes per week, exercised strenuously for less than seven hours per week, and consumed either butter, margarine, or oil on a daily basis were eligible to participate. The participants randomly received either 5 mL per day of fish oil (n=31) or olive oil (n=33). Each participant was also instructed to use fats that were either high in LA (sunflower oil and special margarine) or low LA content (rapeseed oil and rapeseed oil enriched spread). Sixteen and 17 participants received sunflower oil in the olive oil and fish oil group, respectively. Rapeseed oil was provided to 17 participants in the olive oil group and 14 in the fish oil group. Blood samples were collected at baseline, right after the intervention ended, and after eight weeks of washout. Participants completed weighted four day food logs at baseline and during the final week of the intervention. Two weeks prior to the start of the study, participants were given olive oil and butter, with the intention to standardize their consumption of fat and the fatty acid concentration of their tissues. During this two week period and the intervention period, participants were instructed to restrict their fish intake. They were told to otherwise maintain their usual dietary and lifestyle habits during the study. The median oil
consumption through capsule form was 4.4 mL per day in both groups. This corresponds to 3.1 g of long chain PUFA (1.8 g of EPA, 0.2 g DHA, and 1.1 g DPA) per day in the fish oil group. The olive oil group consumed a median of 3.7 g per day of oleic acid. Participants were told to replace the fats they typically used for baking, cooking and on bread, with the fat provided to them. The estimated median consumption of the fats was 3.4 g (0.0 to 32.5) per day and 10.3 (0.0 to 52.5) g per day of oil. The fats and oils were packaged in similar, neutral containers. Participants had their height, weight, and BP measured, and blood samples collected. Total cholesterol, LDL, HDL, and glucose levels were analyzed. At baseline, anthropometrics, BP, smoking status, and macronutrient intake did not differ significantly between the fish oil and olive oil groups. Those who received sunflower oil had a 7.3 g per day higher intake of LA during the study than those receiving the rapeseed oil ($p < .001$). The ALA intake did not differ significantly between groups. The participants who received sunflower oil consumed more PUFA ($p < .001$), and a slightly lower intake of monounsaturated fat ($p = .02$) than those who received rapeseed oil. Consumption of energy and total saturated fatty acids did not differ between the groups. However, body weight increased 0.7 kilograms (kg) in the participants in the fish oil group who received sunflower oil ($p < .05$). The fish oil supplements increased plasma levels of EPA, DHA, and DPA ($p < .001$). The plasma EPA content was used as a marker for determining compliance, as it correlated with the estimated fish oil consumption from the returned capsule bottles. Consumption of the rapeseed fats increased plasma EPA and DPA slightly. Fish oil supplementation lowered TG levels in 35 of the participants ($p = .04$). Plasma TG was reduced by 51% in the fish oil group who received rapeseed and 19% in the fish oil group that received sunflower oil. Neither the fish oil nor the fat interventions affected the other traditional risk factors for CVD, including TC, HDL, or fasting BP. Researchers concluded that
the fish oil group that received rapeseed oil experienced the most benefits for CVD risk reduction. In subjects who already had low TG levels, fish oil consumption further lowered their postprandial and fasting TG. Researchers also concluded that they may have seen more results if they used slightly older, less healthy participants (Damsgaard et al., 2008).

Researchers of a recent study aimed to compare the effects of a lower dose of Ω-3 FA on endothelial function, lipids, and inflammatory makers in people with moderate hypertriglyceridemia (Skulas-Ray et al., 2011). Healthy people with moderate hypertriglyceridemia, as defined by fasting TG levels between 150 and 500 mg/dL, were recruited by local newspaper advertisements, fliers, and Pennsylvania State University emails. Inclusion criterion included age (21 to 65 years), BMI (20 to 39 kg/m²), and general good health. Potential participants who used tobacco, had HTN, liver or kidney dysfunction, consumed fish, flaxseed, or walnuts more than two times per week, or used lipid-lowering, anti-inflammatory, antidepressant, or blood pressure medication were excluded. Women who were not postmenopausal were also excluded. Of the 280 potential participants who completed medical and lifestyle questionnaires, only 28 were eligible to enroll in the study. This study was a randomized, double-blind, three-period crossover placebo controlled trial. There were eight week treatment periods followed by six week washout periods. During the three treatment periods, subjects received in random order a 0 g per day EPA and DHA capsule (the placebo), 0.85 g EPA and DHA, and 3.4 g of EPA and DHA. The corn oil placebo consisted of 56% linoleic acid, 28% oleic acid, and 12% palmitic acid. Each 1 g capsule of Ω-3 FA contained 465 mg of EPA and 375 mg of DHA. Participants were instructed to exclude sources of Ω-3 FA in their diets during the study, including fatty fish, fish oil supplements, flax containing products, walnuts, and Ω-3 FA enriched eggs. They were also instructed to maintain their body weight
and physical activity level. Two weeks into each phase, participants were contacted to determine their compliance and to resolve related difficulties. Four weeks into each phase, subjects reported to the research center to have their capsule bottles weighed, and to receive new supplies. Fasting blood samples were collected at the beginning of the study and at the end of each treatment period (Skulas-Ray et al., 2011).

The final sample population for this study was 26 participants, as two did not complete the study (23 men, 3 women) (Skulas-Ray et al., 2011). Compliance for all participants during all treatment periods was determined to be 95% by capsule logs and capsule bottle weights. Results indicated that TG levels were significantly lower after the 3.4 g per day EPA and DHA treatment than after the placebo and the 0.85 g of Ω-3 FA treatment periods. The average TG level at baseline was 222.8 ± 56.3 mg/dl. The reduction in TG levels with the 3.4 g of Ω-3 FA was 27% compared with the placebo ($p = .002$) (TG= 173.7 ± 17.5 mg/dl). The 0.85 g dose did not alter TG levels (TG=215.3 ± 17.5 mg/dl). Total cholesterol, LDL, and HDL levels did not differ significantly with any treatment. None of the treatments had any effect on BG, insulin, inflammatory markers, or inflammatory gene expression. On average, the participants with the highest TG levels at the start of the study achieved the greatest percent reduction after treatment with the 3.4 g dose. The Ω-3 FA content of RBCs increased in a dose dependent manner, as expected. This confirmed compliance and uptake of Ω-3 FA into cellular membranes. Following eight weeks of treatment with the 3.4 g dose, the Ω-3 FA index associated with a decreased CVD risk (>8%) was achieved. However, these values were not reflective of the maximum uptake of Ω-3 FA into RBC since the duration of the treatment period was only eight weeks. Researchers attribute the lack of effect of any dose of Ω-3 FA used in this study to the short duration of treatment (Skulas-Ray et al., 2011).
Researchers aimed to compare the effects of dietary intakes of different sources of Ω-3 FA, including ALA and EPA and DHA on atherogenic risk factors in hyperlipidemic patients (Finnegan et al., 2003). Adults, ages 25 to 72 years old who were moderately hyperlipidemic were selected to participate by use of emails to university staff, through local media advertisements, and contact through a database held at Royal Berkshire Hospital in the United Kingdom. Interested participants completed health and lifestyle questionnaires, including a FFQ, and provided a blood sample. This study was limited to participants who were not prescribed medication for hypolipidemia or for inflammation, who were not diagnosed with CVD or DM, who consumed less than two portions of oily fish per week, who were not vegetarians, and who were consumers of margarine (Finnegan et al., 2003).

This was a double-blind, placebo-controlled study that was comprised of three cohorts of 50 participants each (Finnegan et al., 2003). The participants were assigned to one of five dietary intervention groups by stratified randomization. These groups included the 0.7 and 1.5 g per day of EPA and DHA (through consumption of fish oil enhanced margarine); 5.0 and 10.0 g of ALA per day (rapeseed and linseed oil margarine); and the control group. The groups receiving the fish oil margarine consumed three capsules of Ω-3 FA to reach the daily target consumption researchers desired, while all other groups received a placebo. The groups were matched for fasting TG levels, age, and gender. Participants were instructed to replace their usual margarine and butter with 25 g containers of the margarine specially designed for this study. For the first month of the study, all participants consumed the control treatment, which was an Ω-6 FA rich margarine. During the next six months, they consumed the dietary treatment assigned to them. Compliance to the assigned treatment was assessed by the return of used margarine tubs and capsules. Fasting blood samples and weight were taken before the study
started, and after two, four, and six months. The blood samples were analyzed for TG, TC, HDL, and FA concentrations (Finnegan et al., 2003).

Results indicated that the proportion of EPA in plasma phospholipid significantly increased compared to baseline levels in the groups that consumed 0.7 and 1.5 g per day of EPA and DHA; however, this was not significantly different from the change in the control group (Finnegan et al., 2003). In contrast, the proportion of ALA in plasma phospholipids was significantly increased in both ALA groups, which was significantly different from the change in the control group. Both EPA and DHA groups were associated with a 15% decrease in mean fasting TG levels after two months of treatment, but not after six months. The ALA intervention did not have a significant effect on total, LDL, or HDL cholesterol compared to the control group. The significance of this study was that researchers compared biologically equivalent amounts of ALA with EPA and DHA. Researchers estimated that 1 g of EPA and DHA would be equivalent to 7 g of ALA in terms of increasing plasma Ω-3 FA concentrations. Although the researchers concluded that dietary ALA was as effective as low-dose preformed EPA and DHA at increasing EPA plasma proportions, ALA consumption did not increase plasma phospholipid DHA levels. This suggests that ALA should not be used as a replacement for dietary DHA. Researchers concluded that dietary ALA and EPA and DHA have different physiologic effects relating to atherogenic risk factors (Finnegan et al., 2003).

Researchers determined an association between blood concentrations of individual long-chain Ω-3 FA and risk of nonfatal MI (Sun et al., 2008). The researchers investigated whether Ω-3 FA concentration of tissues is affected by diet and metabolism. This case control study, which was conducted among the nurses from the Nurses’ Health Study, focused on the plasma content of EPA, DPA, and DHA. The nurses who provided blood samples and were free of
cancer (CA) and CVD at the time of phlebotomy were included. One hundred forty-six nonfatal MIs were documented during the six years of follow up. For each case, two controls were selected. The controls were matched for age (± one year), smoking status, and fasting status at the time of blood sampling. Participants who reported MI were asked for medical records to confirm the diagnosis. The study physicians who reviewed these records were blinded to exposure status of the participants. When medical records were unavailable, the diagnosis was accepted if supported by telephone interview. Of the 146 reported cases of MI, 143 were confirmed by medical records. Validated questionnaires were used to assess medical history, lifestyle risk factors, and dietary habits. Dietary habits were reassessed every four years during the Nurses’ Health Study. The four questions concerning fish intake on the questionnaire were used by researchers to estimate dietary consumption of the long-chain Ω-3 FAs, including EPA, DHA, and DPA. Omega 3 FA intake from supplements was also assessed. Total cholesterol, HDL, and TG levels were measured. Nurses who suffered nonfatal MIs tended to have higher BMIs, consume less alcohol, and were more likely to have a history of HTN than those who did not suffer a nonfatal MI. These factors were adjusted for in the analysis by researchers. Spearman rank coefficients were determined for confounding variables, including energy intake, age, smoking status, BMI, fasting status, postmenopausal status, and postmenopausal hormone use (data not shown) (Sun et al., 2008).

Results indicated that cases had less favorable plasma lipoprotein profiles than controls. (Sun et al., 2008). Both DHA and EPA in blood and RBCs were correlated with dietary consumption of fish and dietary long-chain Ω-3 FA. This was in contrast with DPA. Plasma EPA content was significantly associated with reduced risk of nonfatal MI, as participants in the highest plasma EPA and DHA quartile had a 77% and 60% lower risk of nonfatal MI,
respectively, than those in the lowest quartile (95% CI for both trends, \( p = .001 \) and \( p = .004 \), respectively). After adjustment, neither plasma DHA nor RBC DHA content was significantly associated with risk of nonfatal MI. Researchers also determined associations between \( \Omega-3 \) FA and CVD risk factors. All long chain \( \Omega-3 \) FA, except DPA and DHA, in RBCs were significantly inversely associated with TG levels. Plasma EPA and DPA were positively associated with HDL. Since higher concentrations of EPA and DPA in plasma were associated with reduced risk of nonfatal MI, researchers believe that these findings partially reflect dietary consumption, but also may reflect differences in metabolism of DPA, DHA, and EPA.

Researchers considered DHA in plasma or RBCs to be a stronger indicator of dietary fish and long chain \( \Omega-3 \) FA consumption than EPA. Plasma concentrations of EPA can be influenced by nondietary factors. Eicosapentaenoic acid is metabolized, mobilized and incorporated into the bloodstream at a higher rate than DHA. This study provided evidence that plasma EPA and DPA levels are associated with a reduced incidence of nonfatal MI in women. Plasma concentrations of \( \Omega-3 \) FA reflect dietary consumption and metabolism, and may have additional important effects on CVD risk other than the antiarrhythmic effects confirmed in previous studies (Sun et al., 2008).

Another study determined whether increasing dietary \( \Omega-3 \) FA intake to 1 g per day would have beneficial cardiovascular benefits (Murphy et al., 2007). Eighty-six overweight men and women aged 20 to 65 years old who had fasting TG levels greater than 16 mmol/l participated in this double-blind, randomized study. Participants were recruited through media advertisements in Australia. Interested participants diagnosed with DM or heart disease, those with a history of MI or stroke, or those who consumed more than one fish meal per week or took fish oil supplements were excluded. The participants were stratified according to their initial TG levels.
and BMI, and were randomly assigned to one of two groups, the control group and the Ω-3 FA group. Participants were instructed to consume eight servings per day of foods designated for this study for six months, and to keep food logs. The control foods included; cheese spreads, eggs, chocolate, milk, dips, instant oats, muffins, pancakes, biscuits, salad dressing, and dry soup mix. For each control food, there was a similar food enriched with Ω-3 FA from cod fish oil. Researchers estimated that each serving of these Ω-3 FA enriched foods contained 125 mg of EPA and DHA. The target consumption of eight servings per day was estimated to provide 1 g of Ω-3 FA. Participants were counseled on how to incorporate the eight servings into their typical diets. They were monitored every two weeks for body weight, and they had an opportunity to discuss any problems with following the diet they were assigned. Also, subjects visited the clinic for two consecutive days at the beginning of the trial, after three months, and after six months, to have their BMI calculated, have their waist circumference and hip circumference measured, and to provide a fasting blood sample. They completed a diet history questionnaire and a three day weighted food record three times throughout the study (Murphy et al., 2007).

Results indicated that the participants’ body weight increased 1.1% after three months, and 1.8% after six months; however, there was no significant difference in weight gain between groups (Murphy et al., 2007). Twelve participants withdrew from the study due to dislike of foods provided, leaving 36 participants in the control group and 38 in the Ω-3 FA group. It was estimated through viewing of participants’ food logs that both groups consumed between 6 and 7.5 servings per day of foods designated for this study. There were no significant differences in Ω-3 FA intake between the groups prior to the start of the study. While there was no significant change in Ω-3 FA intake for the control group during the study, Ω-3 FA intake increased in the
Ω-3 FA group from 0.2 g to 1 g per day. There was no significant change in the Ω-3 FA group and control group after three and six months of intervention in SBP, DBP, compliance of small or large arteries, BG, HDL, LDL, TC, and TG. However, there was a significant correlation between calculated intake of Ω-3 FA intake from foods and erythrocyte levels of Ω-3 (r=0.35 at three months and 0.69 at six months, p < .001). This reflects the progressive incorporation of Ω-3 into erythrocytes. Erythrocyte Ω-3 levels were inversely associated with C-reactive protein (CRP) levels, which is an indicator of systemic inflammation, and is also a predictor of cardiovascular risk. After mixed model analysis, there were positive associations between both erythrocyte Ω-3 and small artery compliance (p = .07) and LDL-C (p = .07) that approached significance. Researchers believed that any beneficial effect of Ω-3 may have been masked by the participants’ weight gain. The reason for the lack of change in BP in the Ω-3 FA group may be because of the low intake of Ω-3 FA. Researchers concluded that regular consumption of Ω-3 FA over a six month period increased erythrocyte Ω-3 levels, but did not appear to affect plasma lipids, BP, or arterial compliance (Murphy et al., 2007).

**Hypertension (HTN)**

Hypertension is defined as persistently elevated arterial BP (Couch & Krummel, 2008). It is estimated that one in three Americans has high BP. Blood pressure is defined as the force exerted per unit area on artery walls. In order to be diagnosed with HTN, an individual’s SBP must be 140 mm Hg or higher and the DBP must be at least 90 mm Hg or higher. If HTN is left untreated, it may cause the development of degenerative diseases, including heart failure, end stage renal disease, and peripheral vascular disease (Couch & Krummel, 2008).
Like CHD, HTN is considered a silent disease because many people who have HTN are asymptomatic until they have a potentially fatal heart attack or stroke (Couch & Krummel, 2008). There are three stages of hypertension: pre-hypertension, stage 1, and stage 2. Lifestyle modifications are an important component of treatment during each of these stages. As the disease progresses to stage 2, multiple medications are usually recommended. Regardless of the stage of HTN, controlling BP is essential to reduce the risk of cardiac events. The majority of cases of HTN are multifactorial, and they are due to a combination of genetic and environmental contributors (Couch & Krummel, 2008). There is a strong association between a high BMI (over 30kg/m²) and HTN in both genders. In addition, people who are physically inactive are 30 to 50% more likely to develop HTN as compared to those who are physically active. Furthermore, studies have shown that there is a positive association between dietary sodium consumption and increased BP. Some individuals are salt-sensitive and consumption of sodium in these people may raise their BP to a greater degree. Consumption of at least three alcoholic drinks per day is the threshold for elevating BP. Family history of HTN is also a risk factor (Couch & Krummel, 2008).

Role of Omega 3 Fatty Acids in Prevention of HTN

Omega 3 fatty acids as a supplement to the traditional treatments used for HTN have been gaining national attention. There may be a relationship between consumption of Ω-3 FA and reductions in BP, to a level that is considered low risk for cardiac events. This is the primary goal of treatment for some hypertensive individuals (Couch & Krummel, 2008).

The effects of consumption of dietary sources of Ω-3 FA on BP in hypertensive and non-hypertensive individuals were assessed in a recent study (Ueshima et al., 2007). Participants
included 4,680 men and women, ages 40 to 59 years from Japan, the People’s Republic of China, the United Kingdom, and the United States. Participants’ SBP and DBP were tested eight times throughout the trial during four visits. Twenty-four hour food recalls were obtained at each visit and were converted into nutrient intakes using nutrient intake software. Researchers estimated intakes of dietary sources of Ω-3 FA, such as linoleic acid, EPA, DHA, DPA, and total intake of Ω-3 FA using food data obtained from the participants. The data were adjusted for confounding variables, such as age, gender, and weight. Multiple regression analysis was used to determine if there was an association between participants’ estimated dietary consumption of Ω-3 FA and BP. Researchers concluded that total intake of Ω-3 FA was highest in Japan and lowest in China, as intakes were 1.35% and 0.55% of total calories consumed per day, respectively. Overall, the majority of the estimated consumption of Ω-3 FA was from fish and fish products. Dietary consumption of Ω-3 FA was inversely associated with measures of BP; it was lower in habitual consumers of fish as compared to those who rarely ate fish. The estimated difference in SBP and DBP was between 0.4 to 0.6 mmHg and between 0.5 to 0.6 mmHg, respectively. This inverse association was not significantly stronger for Americans. Subjects who were not hypertensive had observed differences in SBP and DBP that were greater than those who were hypertensive. The estimated effect on BP was small; however, the effect appeared to be larger for non-hypertensive individuals and those who were not on special diets compared to hypertensive individuals (Ueshima et al., 2007). In conclusion, consumption of dietary sources of Ω-3 FA was inversely associated with BP. People who are non-hypertensive may experience a greater change in BP as a result of consuming Ω-3 FA than hypertensive individuals (Ueshima et al., 2007).
Treatment of Cardiovascular Disease

Coronary Heart Disease (CHD)

Therapeutic Lifestyle Changes (TLC) are recommended in the medical nutrition therapy for CHD (Krummel, 2008). Patients who have elevated LDL-cholesterol are initially instructed to follow a prescribed diet, exercise, and reduce their weight in order to meet their target serum lipid levels. Dietary recommendations for TLC include consuming less than 7% of calories from saturated fat and total fat consumption accounting for 25 to 35% of total calories consumed. If beneficial changes are not observed after three to six months of TLC, plant sterols and stanols, fiber, and soy are added to the diet. If this is not successful, patients should start taking medications while still following the prescribed diet plan. The DASH diet, later discussed, is also recommended (Krummel, 2008). In addition, alternative therapies, such as Ω-3 FA supplementation are used as part of the treatment for CHD and its effects are currently being studied.

Role of Omega 3 Fatty Acids in Treatment of CHD

The addition of Ω-3 FA to the traditional treatment options for patients diagnosed with CHD may be beneficial to their health. The AHA recommends that patients diagnosed with CHD consume Ω-3 FA by eating fish weekly or taking supplements daily (Ismail, 2007).

The effect of Ω-3 FA supplementation on markers of endothelial function in people diagnosed with CHD was assessed in a study conducted by Johansen, Seljeflot, Hostmark, and Arnesen (1999). An early indication of atherosclerosis is an altered function and expression of surface molecules in the endothelial cells. Fifty-four patients diagnosed with CHD who previously were included in a larger study were enrolled in this study. Twenty-three consumed
5.1 g of Ω-3 FA per day for six months, while the other 31 participants consumed the same amount of corn oil as a placebo daily. For one month, both groups consumed 5.1 g of Ω-3 FA per day. Researchers concluded that consumption of a highly concentrated Ω-3 FA supplement was associated with decreased levels of homeostatic markers of atherosclerosis; however, consumption of this highly concentrated supplement was also associated with higher values of a proinflammatory response, which may have occurred because of peroxidation. The dose of Ω-3 FA used in this study was more highly concentrated than dietary sources of Ω-3 FA. The $p$ values determined for three markers of endothelial cells, von Willebrand factor, vascular cell adhesion molecule, and tissue plasminogen activator antigen, were statistically significant at 0.05, 0.04, and $<0.01$, respectively. These markers were considered relevant because they are present in the plasma of patients diagnosed with atherosclerotic disease (Johansen et al., 1999). More conclusive studies on the effects of vitamin E supplementation on preventing a proinflammatory response need to be conducted before determining if vitamin E should be supplemented when patients are taking high doses of Ω-3 FA.

In another study, the effects of consumption of fish and dietary long chain Ω-3 FA on heart rate variability (HRV) were examined (Mozaffarian, Stein, Prinas, & Siscovick, 2008). Five thousand, two hundred and one men and women 65 years old and older were randomly selected from Medicare eligibility lists to participate in this study. Using a FFQ, participants indicated how often during the past year they consumed tuna fish, other types of baked or broiled fish, and fried or processed fish products. Researchers focused on determining an association between tuna fish and other types of fish because these were determined to contain Ω-3 FA, which have been associated with a decreased risk of arrhythmic events in prior studies. The EPA and DHA content of consumed fish were estimated from participants’ FFQ. Linear regression
was used to determine whether an association existed for this study. The data were adjusted for covariates, such as age, gender, race, presence of co-morbidities such as DM, and smoking. Information on deaths attributed to CHD according to differences in HRV was evaluated. Participants who were determined to have consumed the greatest amount of fish in the past year also tended to have a higher prevalence of CHD and DM. This may be attributed to dietary recommendations received after diagnosis. However, this association was not determined to be statistically significant. After adjusting the data for demographic variables, lifestyle and dietary choices, and clinical risk factors, tuna and other fish intake were associated with greater HRV indices \( (p < .004) \). During a mean follow up period of 10.8 years, 542 deaths attributed to CHD occurred. This study concluded that usual dietary consumption of fish and tuna fish, both sources of \( \Omega-3 \) FA, were independently associated with optimal HRV. The researchers asserted that fish may have specific effects on different parameters that affect HRV (Mozaffarian et al., 2008).

**Treatment of Hypertension (HTN)**

There are many recommendations for lifestyle modifications to manage HTN (Couch & Krummel, 2008). Weight reduction is recommended, if necessary, to maintain a normal body weight and BMI within the normal range of 18.5 to 24.9 kg/m\(^2\). The DASH diet is usually recommended for patients with HTN (see Appendix I). This diet plan is rich in fruits, vegetables, and low fat dairy, and it is lower in saturated and total fat. Patients are also instructed to reduce their consumption of dietary sodium to consume 2.4 g per day or less. The new dietary guidelines for Americans recommend reducing consumption of sodium to less than 2,300 mg per day (Dietary Guidelines for Americans, 2010). The estimated daily intake of
sodium for all Americans over the age of two years is 3,400 mg. The Dietary Guidelines recommend that people ages 51 and older, and people of any age who are African American, have HTN, chronic kidney disease, or DM should reduce their intake of sodium to 1,500 mg per day. The 1,500 mg per day recommendation includes almost half of the United States population, including children, but mostly adults. These suggestions are based on evidence that on average, people who consume high amounts of sodium have higher blood pressure than those who consume less sodium. This evidence is strongly supported for adults, and moderately supported for children (Dietary Guidelines for Americans, 2010). Patients are also encouraged to engage in at least 30 minutes of physical activity per day most days of the week, such as walking. Moderation of alcohol consumption to no more than two drinks per day for men and no more than one drink per day for women is also recommended.

In recent years, there has been an increased interest in alternative therapies to manage HTN. Patients who are pre-hypertensive are encouraged to adopt the above lifestyle and diet modifications. Patients who are diagnosed with stage 1 HTN usually take one medication/day, while those with stage 2 HTN usually take two medications/day, such as a diuretic and a beta blocker (Couch & Krummel, 2008). Supplementation of the diet with Ω-3 FA is one alternative therapy to treat HTN.

**Role of Omega 3 Fatty Acids in the Treatment of Hypertension**

The effectiveness of Ω-3 FA in treating HTN continues to be studied. In one study, the effect of fatty fish and lean fish intake on BP, fatty acid composition of serum lipids, and cardiovascular risk factors in patients diagnosed with CHD who are taking multiple medications was accessed (Erkkilä et al., 2008). Patients under the age of 70 years of age who were
hospitalized in Kuopio University Hospital due to MI or unstable ischemic attack three months to three years prior to baseline were contacted to participate in this trial. Participants had to be taking beta blockers, be less than 70 years old at baseline, and have normal sinus rhythm in order to participate. The 35 eligible participants were instructed by a Registered Dietitian on how to follow a diet recommended for patients with CHD. They were instructed to consume 100 to 150 g of fish per meal at least four times per week. The patients were randomly divided into groups: one group consumed fatty fish, another consumed lean fish, and the control group consumed lean meats and less than one fish meal per week. Participants in each group were advised not to take fish oil supplements during this intervention study. Seven day food logs were completed during weeks three and seven to determine the subjects’ compliance. Total cholesterol, LDL, HDL, and triglyceride levels were tested four times throughout the trial after fasting for 12 hours. Results showed that reductions in BP were associated with the lean fish group, but not in the fatty fish group ($p < .05$). At screening, the mean SBP and DBP of subjects in the lean fish group were 126 ± 11 and 84 ± 9 mmHg, respectively. After eight weeks, the mean SBP and DBP decreased in the lean fish group by 3.5 ± 3.2 and by 4.6 ± 3.6%, respectively. Lean fish provided smaller amounts of Ω-3 FA than fatty fish. No significant changes in total- and LDL-cholesterol or HRV were observed for any group. The observed increase in HDL cholesterol in the Ω-3 FA fish group and decrease in the control group were not considered significant. Researchers observed that consumption of fatty fish, which contained higher amounts of Ω-3 FA than lean fish, did not decrease BP, TC, LDL, or HRV. However, intakes of lean fish were associated with reductions in BP. In conclusion, consumption of fatty fish at least four times per week was associated with increased proportions of both EPA and DHA in serum lipids (Erkkilä et al., 2008).
Discussion

The studies used in this literature review focused on the effectiveness of \( \Omega-3 \) FA for the prevention or treatment of CVD, specifically CHD and HTN (see Appendix I). The studies included \( \Omega-3 \) FA from various sources, including fish, fish oil, flaxseed, supplements, or enriched foods. The studies also had differing doses of \( \Omega-3 \) FA (see Appendix II). Overall, dietary or supplemental \( \Omega-3 \) FA consumption either had no significant effect or a positive effect on various measures of CVD. Many of the studies reviewed found an inverse association between fish or \( \Omega-3 \) FA and incidence of or mortality from CVD.

Role of Omega 3 Fatty Acids in Prevention of CHD

Omega three fatty acids may have different effects on the various predictors of CHD development, including: HRV, endothelial function, low HDL levels, and high BP, HDL, TG, and LDL levels. Studies have also focused on the association between fish and \( \Omega-3 \) FA intake and risk of MI, which is another manifestation of CHD. The studies used for this literature review differ in the source of \( \Omega-3 \) FA, in dietary or supplemental forms, and the dose of \( \Omega-3 \) FA consumed.

The study by Dyerberg et al. (2004) determined that after eight weeks of consuming a PUFA enriched diet, only minor decreases in arterial BP, SBP, DBP, and TG levels were observed. The researchers were unable to determine a beneficial effect of PUFA consumption on HRV or endothelial function. However, a weakness of this study is that participants were considered healthy and had normal BP levels prior to the start of the study. Another limitation of this study was the short duration of the trial, which was only eight weeks, and there was no further follow up.
A study by Yamagshi et al. (2008) found that fish and Ω-3 FA intake were inversely associated with risk of mortality from heart failure and total CVD (Yamagashi et al., 2008). This study had many limitations. One limitation was that the data collected only included mortality from heart diseases, rather than incidence of heart disease. Another limitation was that the basis of this study, which was the estimated fish and Ω-3 FA intake, was determined from self-reported FFQ, which may have been inaccurate (Yamagashi et al., 2008).

Researchers of the Nurses’ Health Study also determined an inverse association between fish and Ω-3 FA intake and death from CHD, which was somewhat stronger for fatal CHD than for nonfatal MI (Hu et al., 2002). The strengths of this study included the large sample size of 84,688 nurses, and that fish consumption was assessed multiple times throughout the study, which accounted for changes in dietary patterns. Also, the study had a long follow up period that lasted for 16 years. As in the study by Yamagashi et al. (2008), a limitation of this study is that the participants completed their own FFQ. The results of the study by Asherio et al. (1995) are not in agreement with these findings, as these researchers found no evidence of an association between consumption of fish or marine Ω-3 FA and risk of CHD or MI.

Researchers of a cohort study determined associations between fish, EPA, and DHA intake and risks of CHD and MI (Goede, Geleijnse, Boer, Kromhout, & Verchuren, 2010). Participants in the highest quartile for EPA consumption had the lowest risk for fatal CHD. However, as in the study by Hu et al. (2002), consumption of Ω-3 FA was not associated with nonfatal MI. The researchers’ conclusion that higher consumption of fish was associated with reduced risk for fatal CHD and fatal MI was in accordance with the findings of Hu et al. (2002). The strengths of this study were the large number of participants (n=22,654), the small loss of participants to follow up, long mean follow up period of 11.3 years, and consideration of
confounding variables. The weaknesses were that data on physical activity were available for only 77% of participants. Researchers also concluded that misclassification of participants in terms of fish and EPA and DHA intake may have occurred.

Researchers of another study also observed associations between fish consumption and decreased risk of CVD (Streppel et al., 2008). Participants who consumed the mean amount of fish per day had a lower risk of death from CHD than nonconsumers of fish. Researchers observed a significant and positive interaction with age for the association between long term fish intake or EPA and DHA intake with CHD death. These associations became weaker as age increased. After age 70, researchers were unable to draw conclusions because the confidence intervals were too wide. The strengths of this study were the long duration of follow up, and the collection of detailed information regarding dietary intake on seven different occasions during the study. Researchers were able to use information on past, recent, and long term fish consumption. The length of follow up allowed them to study interactions with age. The weaknesses of this study were that the number of sudden coronary deaths may have been too low to determine a dose-dependent association for EPA and DHA. Information regarding pre-study intakes of fish was not available for some of the participants (Streppel et al., 2008).

A recent study by Barceló-Coblijn et al. (2008) compared the cardiovascular related effects of consumption of flax and fish oil in firefighters. Results showed that the ALA blood concentrations in those receiving the highest dose of flax oil increased significantly compared to the control group, until week eight of the study. After the eighth week, ALA content slightly decreased, which researchers believed represented the conversion of ALA to EPA to DHA. No significant changes between groups were determined with respect to TC, TG, or HDL; however, this may be reflective of the doses provided. The results of this study indicate that the observed
effects of flax and fish oil consumption had maximum effects after six to eight weeks of treatment (Barceló-Coblijn et al., 2008).

Another recent study focused on the effectiveness of flaxseed consumption on reducing risk factors for CVD (Bloedon et al., 2008). Researchers concluded that flaxseed consumption significantly lowered HDL levels in hypercholesterolemic men, but not in women. This is not in accordance with the study by Barceló-Coblijn et al. (2008), in which HDL was not significantly affected by flax consumption. Some participants experienced AE after consuming baked goods that each contained 20 grams of ground flaxseed (Bloedon et al., 2008). Researchers found that flaxseed consumption significantly increased plasma levels of Ω-3 FA, ALA, and DPA. The flaxseed group had reduced LDL levels by week five, but these changes were not significant at week ten. A decrease in adherence to the intervention and diet, or biological adaptation can explain this finding. This result is in agreement with other related trials, in which flaxseed consumption up to six weeks had a significant LDL reducing effect, but studies that lasted longer than ten weeks did not report reductions in LDL levels. A weakness of this study was the short duration and small number of participants (Bloedon et al., 2008).

Another study aimed to compare the effects of consumption of fish and fish-oil supplements on the Ω-3 FA content of RBCs and PPLs (Harris et al., 2007). Researchers concluded that EPA and DHA content of RBCs and PPLs did not differ significantly when equivalent doses of Ω-3 FA from fish and fish oil capsules were consumed. The EPA and DHA concentrations increased more quickly in PPL than in RBCs, which confirms previous findings that turnover of EPA and DHA in plasma occurs more quickly than in RBCs. However, after the first month of treatment, the concentrations of EPA in RBCs did not differ significantly between the groups. Weaknesses of this study include the small sample size, and that fish and fish
capsule consumption was not directly supervised. Various doses of Ω-3 FA were not used in this study. Researchers suggest that the weaknesses of the study design could have been corrected by including men and women, a larger variety of ages, and a longer duration (Harris et al., 2007).

In a recent study, researchers assessed the effects of fish oil consumption in addition to high or low intakes of linoleic acid (LA) on risk factors for CVD (Damsgaard et al., 2008). A strength of this study is that two weeks before the start of the study, participants were given olive oil and butter to standardize their consumption of fat and the FA concentration of their tissues. The fish oil supplements significantly increased plasma levels of EPA, DHA, and DPA. Plasma TG levels were reduced in participants consuming fish oil. Neither the fish oil nor the fat interventions affected the other traditional risk factors for CVD, including TC, HDL, or fasting BP. Body weight increased in the participants in the fish oil group and researchers believed that weight gain may have negated the beneficial effects of the fish oil consumption. Researchers also concluded that they may have seen more positive results if they used slightly older, less healthy participants. A strength of this study is that participants completed weighted four day food logs, which may be more accurate at determining the amount of food consumed than an unweighted food log (Damsgaard et al., 2008).

Researchers of a recent study aimed to compare the effects of a lower dose of Ω-3 FA on endothelial function, lipids, and inflammatory makers in people with moderate hypertriglyceridemia (Skulas-Ray et al., 2011). A strength of this study was the crossover design, so that subjects received all of the various doses provided of EPA and DHA by the end of this study. Another strength is that participants were instructed how to maintain their body weight and physical activity level, which helped to prevent the weight gain observed in the study by Damsgaard, Anderson, and Lauritzen (2008). However, the final sample population for this
study was small (Skulas-Ray et al., 2008). Results indicated that TG levels were significantly lower in the group receiving the highest dose of EPA and DHA. The participants with the highest TG levels at the start of the study tended to achieve the greatest percent reduction after treatment with the highest dose of EPA and DHA. Similarly to Damsgaard et al. (2008), TC, LDL, and HDL levels did not differ significantly with any treatment. Limitations of this study include the predominantly male sample, and short treatment duration (Skulas-Ray et al., 2011).

Researchers aimed to compare the effects of dietary intakes of different sources of Ω-3 FA, including ALA and EPA and DHA on atherogenic risk factors in hyperlipidemic patients (Finnegan et al., 2003). The proportion of ALA in PPLs was significantly increased in both ALA groups. Both EPA and DHA groups were associated with a decrease in mean fasting TG levels after two months of treatment, but not after six months. The ALA intervention did not have a significant effect on total-, LDL-, or HDL-cholesterol compared to the control group. The significance of this study was that researchers compared biologically equivalent amounts of ALA with EPA and DHA. Although the researchers concluded that dietary ALA was as effective as low-dose preformed EPA and DHA at increasing EPA plasma proportions, ALA consumption did not increase DHA levels in PPLs. This suggests that ALA should not be used as a replacement for dietary DHA. The results of this study indicate that dietary ALA and EPA and DHA have different physiologic effects relating to atherogenic risk factors (Finnegan et al., 2003).

Researchers determined an association between blood concentrations of individual long-chain Ω-3 FA and risk of nonfatal MI (Sun et al., 2008). Both DHA and EPA in blood and RBCs were correlated with dietary consumption of fish and dietary long-chain Ω-3 FA; however, this was not observed with DPA. Plasma EPA content was significantly associated with reduced
risk of nonfatal MI. After adjustment, neither plasma nor RBC DHA content was significantly associated with risk of nonfatal MI. Plasma EPA and DPA were positively associated with HDL.

Another study determined whether increasing dietary Ω-3 FA intake to one gram per day would have beneficial cardiovascular benefits (Murphy et al, 2007). There was no significant change in the Ω-3 FA group after three and six months of intervention in SBP, DBP, compliance of small or large arteries, BG, HDL, LDL, TC, and TG. Researchers believed that any beneficial effect of Ω-3 may have been masked by the participants’ weight gain. The reason for the lack of change in BP in the Ω-3 FA group may be because of the low intake of Ω-3 FA (Murphy et al., 2007).

**Role of Omega 3 Fatty Acids in Prevention of HTN**

The effects of consumption of dietary sources of Ω-3 FA on BP in hypertensive and non-hypertensive individuals was assessed in a recent study (Ueshima et al., 2007). Total dietary consumption of Ω-3 FA was independently and inversely associated SBP and DBP. Subjects who were not hypertensive had observed differences in SBP and DBP that were greater than those who were hypertensive. The estimated effect on BP was small, and the inverse relationship between Ω-3 FA and BP was considered by researchers to be weak (Ueshima et al., 2007).

**Role of Omega 3 Fatty Acids in Treatment of CHD**

Johansen et al. (1999) studied the effect of Ω-3 FA supplementation on markers of endothelial function in people diagnosed with CHD. Researchers concluded that consumption of
a highly concentrated Ω-3 FA supplement was associated with decreased levels of homeostatic markers of atherosclerosis; however, consumption of this highly concentrated supplement was also associated with higher values of a proinflammatory response. However, the supplement used in this study was highly concentrated, and this dose might induce peroxidation more easily than a lower dose. The dose of Ω-3 FA used in this study was more highly concentrated than dietary sources of Ω-3 FA.

Mozaffarian et al. (2008) studied the effects of consumption of fish and dietary long chain Ω-3 FA on HRV. After adjusting the data for demographic variables, lifestyle and dietary choices, and clinical risk factors, tuna and other fish intake were associated with greater HRV indices. Researchers concluded that usual dietary consumption of fish and tuna fish were independently associated with optimal HRV. This result was not in agreement with the results of Dyerberg et al. (2004) and Johansen et al. (1999). The researchers determined that fish may have specific effects on different parameters that affect HRV (Mozaffarian et al., 2008).

Role of Omega 3 Fatty Acids in the Treatment of Hypertension

Erkkilä et al. examined the effect of fatty fish and lean fish intake on BP, FA composition of serum lipids, and CVD risk factors in participants diagnosed with CHD who were taking multiple medications (2008). A strength of this study was that the participants were instructed by a Registered Dietitian on how to follow a diet recommended for patients with CHD throughout the study. No significant changes in total- and LDL-cholesterol or HRV were observed for participants consuming lean or fatty fish. Results showed that reductions in BP were associated with the lean fish group, but not the fatty fish group. These results were not expected because lean fish provides smaller amounts of Ω-3 FA than fatty fish. Researchers
observed that consumption of fatty fish did not decrease BP, TC, LDL, or HRV. However, the study was short in duration and may not have allowed enough time to observe differences in heart rate (Erkkilä et al., 2008).

**Coronary Heart Disease**

The results of the studies used for this literature review were not always in agreement. Dyerberg et al. (2004) and Johansen et al. (1999) found no association between markers of HRV and fish or Ω-3 FA, which was not in agreement with the results of Mozaffarian et al. (2008). Yamagashi et al. (2008), Hu et al. (2002), Goede et al. (2010), and Streppel et al. (2008) found an association between fish or Ω-3 FA consumption and reduced risk of mortality from CVD related causes. However, Asherio et al. (1995) found no association between consumption of fish or marine Ω-3 FA and risk of CHD or risk of MI. Barceló-Coblijn et al. (2008), Damsgaard, et al. (2008), and Murphy et al. (2007) concluded that flax oil, fish oil, or Ω-3 FA consumption did not affect TC, TG, or HDL levels. However, Skulas-Ray et al. reported significant reductions in TG levels with a high dose of Ω-3 FA (2011). Also, Bloedeon et al. found that flax consumption lowered HDL levels in men (2008). Researchers determined that consumption of fish, fish oil, or Ω-3 FA raised the Ω-3 FA of RBCs (Harris et al., 2007; Murphy et al., 2007).

**Hypertension**

Results showed that reductions in BP were associated with the lean fish consumption and total dietary consumption of Ω-3 FA, respectively (Erkkilä et al., 2008) (Ueshima et al., 2007). Since the results of these studies are mixed, it is possible that consumption of Ω-3 FA will affect various measures involving CVD differently, such as BP, HDL, LDL, TG, endothelial function
and HRV. This may be especially true in different populations, such as healthy people and people already diagnosed with CVD. Consumption of Ω-3 FA in supplemental form or from dietary sources may have also affected the outcomes of these studies. More conclusive studies should be conducted comparing the efficacy of Ω-3 FA vegetarian and fish sources in prevention of CVD or for use as part of a treatment plan. Until more conclusive research is conducted, it may be beneficial for people to follow both traditional and alternative recommendations simultaneously to try and prevent CVD or to treat CVD.

**Conclusion**

Due to the prevalence of and mortality from CVD in the United States, studies have been conducted to determine the causes and effectiveness of treatments, both traditional and alternative. Healthy People 2020 aims to increase awareness for and reduce mortality rates from CVD (Healthy People, 2010). Although there are many proven lifestyle and dietary recommendations to reduce a person’s risk of developing CVD, genetics and older age are two non-modifiable risk factors (Krummel, 2008). Once a patient has been diagnosed with a form of CVD, it is important to reduce that person’s risk of mortality by managing the disease. One alternative treatment that is gaining national attention is the use of Ω-3 FA in the prevention of and treatment for CVD.

The doses of Ω-3 FA used in each of the studies differed (see Appendix II). Barceló-Coblijn et al. (2008) determined that consumption of 2.4 g of flax oil per day was sufficient. Bloedon et al. (2008) observed reductions in HDL levels in men after they consumed 40 g of flaxseeds though enriched products; however, some participants experienced AE. Damsgaard et al. (2008) observed reductions in TG levels with only 5 mL of fish oil. Skulas-Ray et al. (2011)
and Finnegan et al. (2003) observed reductions in TG with 3.4 g and 0.7 or 1.5 g of EPA and DHA, respectively. Erkkilä et al. (2008) observed reductions in BP with consumption of 100 to 150 g of lean fish four times per week. Johansen et al. (1999) observed decreased levels of markers of atherosclerosis with consumption of a 5.1 gram ω-3 FA supplement; however, this was also associated with a proinflammatory response. When deciding which dose of ω-3 FA to consume, it is important to consider the possibility of negative effects, such as AE or a proinflammatory response. Until more conclusive research is conducted on the safety of using higher doses, people not diagnosed with CHD should follow the current recommendation of consuming fatty fish two times per week, and people who are diagnosed with CHD should consume one g per day of EPA and DHA or two to four g from supplements, if under the care of a physician (Ismail, 2007).

As evidenced by this literature review, the results of some studies are not in agreement with others. In all of the studies, consumption of ω-3 FA either had no significant effect or had a mostly positive effect on parameters relating to CHD or HTN.
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## Appendix IA. DASH Eating Plan—Number of Food Servings by Calorie Level

<table>
<thead>
<tr>
<th>Food Group</th>
<th>1,200 Cal.</th>
<th>1,400 Cal.</th>
<th>1,600 Cal.</th>
<th>1,800 Cal.</th>
<th>2,000 Cal.</th>
<th>2,600 Cal.</th>
<th>3,100 Cal.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grains(^a)</td>
<td>4–5</td>
<td>5–6</td>
<td>6</td>
<td>6</td>
<td>6–8</td>
<td>10–11</td>
<td>12–13</td>
</tr>
<tr>
<td>Vegetables</td>
<td>3–4</td>
<td>3–4</td>
<td>3–4</td>
<td>4–5</td>
<td>4–5</td>
<td>5–6</td>
<td>6</td>
</tr>
<tr>
<td>Fruits</td>
<td>3–4</td>
<td>4</td>
<td>4</td>
<td>4–5</td>
<td>4–5</td>
<td>5–6</td>
<td>6</td>
</tr>
<tr>
<td>Fat-free or low-fat milk and milk products(^b)</td>
<td>2–3</td>
<td>2–3</td>
<td>2–3</td>
<td>2–3</td>
<td>2–3</td>
<td>3</td>
<td>3–4</td>
</tr>
<tr>
<td>Lean meats, poultry, and fish</td>
<td>3 or less</td>
<td>3–4 or less</td>
<td>3–4 or less</td>
<td>6 or less</td>
<td>6 or less</td>
<td>6 or less</td>
<td>6–9</td>
</tr>
<tr>
<td>Nuts, seeds, and legumes</td>
<td>3 per week</td>
<td>3 per week</td>
<td>3–4 per week</td>
<td>4 per week</td>
<td>4–5 per week</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Fats and oils(^c)</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2–3</td>
<td>2–3</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Sweets and added sugars</td>
<td>3 or less per week</td>
<td>3 or less per week</td>
<td>3 or less per week</td>
<td>5 or less per week</td>
<td>5 or less per week</td>
<td>≤2</td>
<td>≤2</td>
</tr>
<tr>
<td>Maximum sodium limit(^d)</td>
<td>2,300 mg/day</td>
<td>2,300 mg/day</td>
<td>2,300 mg/day</td>
<td>2,300 mg/day</td>
<td>2,300 mg/day</td>
<td>2,300 mg/day</td>
<td>2,300 mg/day</td>
</tr>
</tbody>
</table>

- \(^a\) Whole grains are recommended for most grain servings as a good source of fiber and nutrients.
- \(^b\) For lactose intolerance, try either lactase enzyme pills with milk products or lactose-free or lactose-reduced milk.
- \(^c\) Fat content changes the serving amount for fats and oils. For example, 1 Tbsp regular salad dressing = one serving; 1 Tbsp low-fat dressing = one-half serving; 1 Tbsp fat-free dressing = zero servings.
- \(^d\) The DASH eating plan consists of patterns with a sodium limit of 2,300 mg and 1,500 mg per day.

### Appendix IB. DASH Eating Plan—Serving Sizes, Examples, and Significance

<table>
<thead>
<tr>
<th>Food Group</th>
<th>Serving Sizes</th>
<th>Examples and Notes</th>
<th>Significance of Each Food Group to the DASH Eating Plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grains&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1 slice bread 1 oz dry cereal&lt;sup&gt;b&lt;/sup&gt; ½ cup cooked rice, pasta, or cereal&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Whole-wheat bread and rolls, whole-wheat pasta, English muffin, pita bread, bagel, cereals, grits, oatmeal, brown rice, unsalted pretzels and popcorn</td>
<td>Major sources of energy and fiber</td>
</tr>
<tr>
<td>Vegetables</td>
<td>1 cup raw leafy vegetable ½ cup cut-up raw or cooked vegetable ½ cup vegetable juice</td>
<td>Broccoli, carrots, collards, green beans, green peas, kale, lima beans, potatoes, spinach, squash, sweet potatoes, tomatoes</td>
<td>Rich sources of potassium, magnesium, and fiber</td>
</tr>
<tr>
<td>Fruits</td>
<td>1 medium fruit ¼ cup dried fruit ½ cup fresh, frozen, or canned fruit ½ cup fruit juice</td>
<td>Apples, apricots, bananas, dates, grapes, oranges, grapefruit, grapefruit juice, mangoes, melons, peaches, pineapples, raisins, strawberries, tangerines</td>
<td>Important sources of potassium, magnesium, and fiber</td>
</tr>
<tr>
<td>Fat-free or low-fat milk and milk products&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1 cup milk or yogurt 1½ oz cheese</td>
<td>Fat-free milk or buttermilk; fat-free, low-fat, or reduced-fat cheese; fat-free/low-fat regular or frozen yogurt</td>
<td>Major sources of calcium and protein</td>
</tr>
<tr>
<td>Lean meats, poultry, and fish</td>
<td>1 oz cooked meats, poultry, or fish 1 egg&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Select only lean; trim away visible fats; broil, roast, or poach; remove skin from poultry</td>
<td>Rich sources of protein and magnesium</td>
</tr>
<tr>
<td>Nuts, seeds, and legumes</td>
<td>½ cup or 1½ oz nuts 2 Tbsp peanut butter 2 Tbsp or ½ oz seeds ½ cup cooked legumes (dried beans, peas)</td>
<td>Almonds, filberts, mixed nuts, peanuts, walnuts, sunflower seeds, peanut butter, kidney beans, lentils, split peas</td>
<td>Rich sources of energy, magnesium, protein, and fiber</td>
</tr>
<tr>
<td>Fats and oils&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1 tsp soft margarine 1 tsp vegetable oil 1 Tbsp mayonnaise 2 Tbsp salad dressing</td>
<td>Soft margarine, vegetable oil (canola, corn, olive, safflower), low-fat mayonnaise, light salad dressing</td>
<td>DASH study had 27% of calories as fat, including fat in or added to foods</td>
</tr>
<tr>
<td>Sweets and added sugars</td>
<td>1 Tbsp sugar 1 Tbsp jelly or jam ½ cup sorbet, gelatin dessert 1 cup lemonade</td>
<td>Fruit-flavored gelatin, fruit punch, hard candy, jelly, maple syrup, sorbet and ices, sugar</td>
<td>Sweets should be low in fat</td>
</tr>
</tbody>
</table>

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<sup>a</sup> Whole grains are recommended for most grain servings as a good source of fiber and nutrients.

<sup>b</sup> Serving sizes vary between ½ cup and 1¼ cups, depending on cereal type. Check the product’s Nutrition Facts label.

<sup>c</sup> For lactose intolerance, try either lactase enzyme pills with milk products or lactose-free or lactose-reduced milk.
Because eggs are high in cholesterol, limit egg yolk intake to no more than four per week; two egg whites have the same protein content as 1 oz of meat.

Fat content changes the serving amount for fats and oils. For example, 1 Tbsp regular salad dressing = one serving; 1 Tbsp low-fat dressing = one-half serving; 1 Tbsp fat-free dressing = zero servings.

## Appendix II. List of Intervention Studies

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Type of Ω-3 FA</th>
<th>Dose of Ω-3 FA Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murphy et al., 2007</td>
<td>Ω-3 long chain PUFA and cod fish oil enriched foods</td>
<td>Eight servings of study foods provided an estimated 1 g/day</td>
</tr>
<tr>
<td>Bloedon et al., 2008</td>
<td>Flaxseed</td>
<td>20 g of ground flaxseed was baked into study foods. Participants instructed to consume two study foods/day</td>
</tr>
<tr>
<td>Barceló-Coblijn et al., 2008</td>
<td>Flax oil, fish oil</td>
<td>1.2, 2.4, or 3.6 g/day of flax oil. 0.6 or 1.2 g/day of fish oil.</td>
</tr>
<tr>
<td>Johansen et al., 1999</td>
<td>Ω-3 FA supplement</td>
<td>5.1 g/day</td>
</tr>
<tr>
<td>Skulas-Ray et al., 2011</td>
<td>EPA &amp; DHA supplement</td>
<td>0.85 g/day, 3.4 g/day</td>
</tr>
<tr>
<td>Dyerberg et al., 2004</td>
<td>Fish oil</td>
<td>12 g fish oil/day, with approximately 4g Ω-3 FA</td>
</tr>
<tr>
<td>Erkkilä et al., 2008</td>
<td>Fatty fish, lean fish</td>
<td>100-150 g of fish, minimum of 4 times/week</td>
</tr>
<tr>
<td>Damsgaard, Frøkjaer, Anderson, &amp; Lauritzen, 2008</td>
<td>Fish oil</td>
<td>5 mL/day</td>
</tr>
<tr>
<td>Harris et al., 2007</td>
<td>Fish, fish capsule</td>
<td>Three six oz. cans of tuna &amp; 171 g fillet of salmon every two weeks, 1-2 capsules/day (86±2 mg EPA &amp; 311±12mg DHA/capsule)</td>
</tr>
<tr>
<td>Finnegan et al., 2003</td>
<td>Fish oil margarine, rapeseed/linseed oil margarine</td>
<td>0.7 or 1.5 g EPA &amp; DHA/day, 5.0 or 10.0 g ALA/day</td>
</tr>
</tbody>
</table>

Ω-3= omega 3; Ω-3 FA= omega 3 fatty acids; PUFA= polyunsaturated fatty acids; DHA= docosahexaenoic acid; EPA= eicosapentaenoic acid; ALA= alpha-linolenic acid