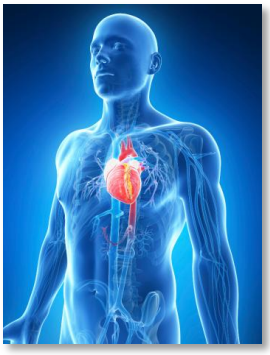
CORONARY HEART DISEASE AND THE COST EFFECTIVENESS OF OMEGA-3 AND B VITAMIN DIETARY SUPPLEMENTATION



The total health care expenditure for managing and treating CHD for the total U.S. population exceeds $100 billion per year, and the expenditure for all U.S. adults over the age of 55 with CHD exceeds $60 billion per year.

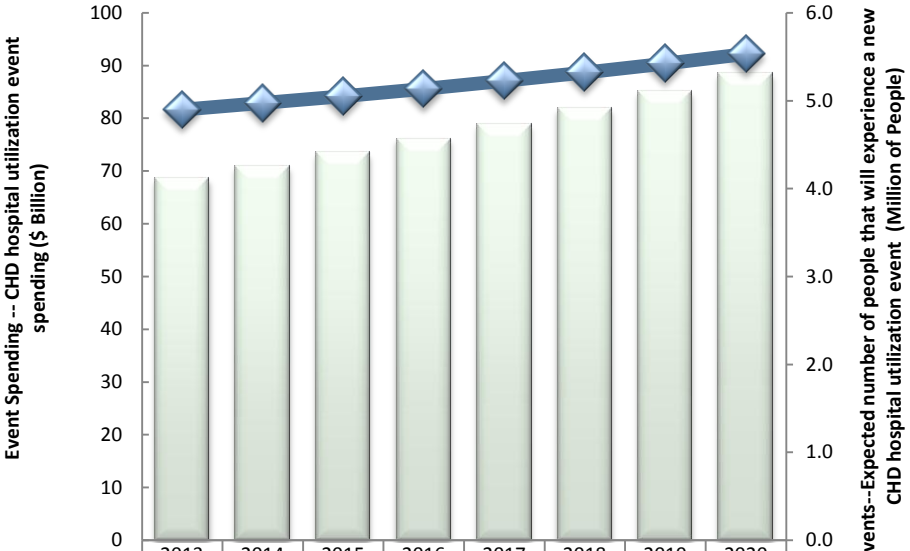
Prevalence and Social Consequences

Coronary heart disease (CHD) is defined as the set of conditions that causes the accumulation of plaque in the coronary arteries, thereby restricting blood flow to the heart and potentially resulting in angina, arrhythmia, myocardial infarction (MI), and heart failure (National Institutes of Health, 2012). CHD puts a heavy burden, both financially and in terms of quality of life, on the citizens of the United States. In addition, Americans are increasingly struggling to cope with its increasing prevalence, as well as the consequential increasing costs of treating this disease condition. CHD is the leading cause of death in the United States, causing 385,000 deaths each year and accounting for 1 out of 6 deaths, according to the Centers for Disease Control and Prevention (CDC) (National Health and Nutrition Examination Survey, 2013). In fact, 6.6% of the total adult U.S. population is reported to have CHD, and its prevalence sharply increases with age: more than 16% of adults over the age 55 are estimated to have heart disease (National Health and Nutrition Examination Survey, 2013). Furthermore, the hospital utilization expenditures related to managing and treating CHD for the total U.S. population exceed $100.00 billion per year, and expenditures for all U.S. adults over the age of 55 with CHD exceed $60.00 billion per year, according to the Center for Financing, Access and Cost Trends, Agency for Healthcare Research and Quality's Medical Expenditure Panel Survey 2010 and Frost & Sullivan analysis (Agency for Healthcare Research and Quality—MEPS).

A significant portion of this cost is related to events that require expensive hospital services, specifically inpatient procedures and emergency room visits. According to MEPS data and Frost & Sullivan's analysis, the expenditures on inpatient procedures and emergency room visits for all U.S. adults over the age of 55 with CHD exceeded $64.00 billion in 2012 (Agency for Healthcare Research and Quality—MEPS). This equates to a mean per person expenditure on CHD-related inpatient procedures and emergency room visits of $13,317.

The total cumulative direct health care costs related to CHD events among all U.S. adults over the age of 55 diagnosed with CHD is expected to be over $600 billion from 2013 to 2020.

Figure 3.1—Total Expenditure Forecast for CHD-related Events among All U.S. Adults Over the Age of 55 with CHD, 2013–2020



	2013	2014	2015	2016	2017	2018	2019	2020
Event spending ($ B)	68.51	70.89	73.40	76.08	78.92	81.91	85.12	88.50
Events (M People)	4.90	4.97	5.05	5.14	5.23	5.32	5.42	5.53

Note: All figures are rounded. Source: Frost & Sullivan analysis.

Projecting these per-person expenditures forward at an annual growth rate of 5% from 2013 to 2020 and assuming an annual target population growth rate of 1.7% during the same period, it is expected that an average of 5.2 million adults over the age of 55 who have been diagnosed with CHD will experience a costly CHD event, defined as all inpatient hospitalizations and emergency room visits from 2013 to 2020, at an annual average $16,690 cost per person. This implies that the total cumulative direct health care costs related to CHD events among all U.S. adults over the age of 55 diagnosed with CHD will be $623.33 billion over the forecast period; additionally, the average direct health care costs related to CHD events among this target population will be nearly $77.92 billion per year.

Figure 3.2—Coronary Heart Disease Cost Summary Statistics for All U.S. Adults Over the Age of 55, 2012–2020

Metric	Measure
Population with CHD (people at high risk of experiencing an event), million people[2]	17.02 M
Number of people who experienced a CHD-related inpatient procedure and/or visited the emergency room, 2012, million people	4.83 M
Event rate—percent of the high risk population that will experience a CHD event, (ER)	16%
CHD hospital utilization event spending (inpatient procedures and emergency room visits), 2012[3]	$64.34 B
Expected average annual CHD hospital utilization event spending (inpatient procedures and emergency room visits), 2013–2020	$77.92 B
Cumulative CHD hospital utilization event spending (inpatient procedures and emergency room visits), 2013–2020	$623.33 B
Average claimed expenditures per person, 2012	$13,317
Expected average claimed expenditures per person per year, 2013–2020	$16,690

Source: Summary Health Statistics for U.S. Adults: National Health Interview Survey 2011—Centers for Disease Control and Prevention, Center for Financing, Access and Cost Trends—Agency for Healthcare Research and Quality; Medical Expenditure Panel Survey, 2010 and Frost & Sullivan

One way to control the burden of CHD costs is to minimize the number of costly inpatient procedures and emergency room events. Thus, prevention of an event is critical in lowering the demand for disease management services.

CHD is partially preventable because it is caused, in part, by a person's lifestyle choices. The scientific consensus states that high blood pressure, high LDL cholesterol, and smoking are the leading risk determinants for CHD. High blood pressure and high LDL cholesterol are determined in part by lifestyle choices related to poor diet, physical inactivity, and alcohol use (Division for Heart Disease and Stroke Prevention, 2013). Thus, changing lifestyle choices is an important option to minimize CHD-related events that a person might experience and pay for. Changing diet is a critical step in decreasing one's chance of experiencing a costly event; there has been increasing research in understanding the exact role that key dietary supplements have in helping to lower a person's odds of experiencing a CHD event.

CHD is partially preventable because it is caused, in part, by an individual's lifestyle choices. Thus, changing lifestyle choices is an important option to minimize the number of CHD-related events that an individual might experience and, consequently, pay for.

2 Includes all coronary heart disease, angina pectoris, heart attack, or any other heart condition or disease events

3 An event is defined as any claimed treatment or disease management activity that requires expenditure to be paid out-of-pocket, by private insurance companies, or by Medicare or Medicaid and includes all hospital inpatient stays and emergency room visits as defined by the Center for Financing, Access and Cost Trends, Agency for Health Care Research, and Quality: Medical Expenditure Panel Survey

It is expected that omega-3 marine fatty acids might reduce CHD by regulating cell membrane properties or through intracellular signal transduction.

Many dietary supplement products are available that have been shown to have positive effects on heart health. This chapter explores the possible economic effect derived from using omega-3 fatty acids or from using three B vitamins (folic acid, B6, and B12) through avoided hospitalization expenditures associated with CHD events. Specifically, this assessment uses the D-L random-effects literature review approach to determine the deduced consequential effect of using omega-3 or of using B vitamins on the chance of experiencing a costly CHD event; additionally, possible net cost-savings have been calculated.

Omega-3

Literature Review

The term omega-3 fatty acids refers to a class of omega-3 polyunsaturated fatty acids found primarily in marine sources (such as fish and algae) and in certain plant sources. The marine omega-3s eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are the ones primarily studied in the context of reducing the risk of many health conditions, including CHD (Memorial Sloan-Kettering Cancer Center, 2013). The underlying mechanisms by which omega-3 might reduce CHD are subjects of ongoing research; however, it is expected that these compounds may have roles in regulating cell membrane properties or intracellular signal transduction (Memorial Sloan-Kettering Cancer Center, 2013). Regarding the recommended daily intake of omega-3 dietary supplements, there is no U.S. government-recognized recommended daily intake level (Institute of Medicine, 2006). However, the American Heart Association recommends that patients with documented CHD consume about 1 gram of EPA and DHA per day, preferably from fish (Kris-Etherton, Harris, & Appel, 2002).

To deduce the expected efficacy of a treatment with omega-3 on the occurrence of a CHD event, a systematic search was conducted that focused on published studies that tested for and quantified the effect of omega-3 supplementation on the incidence of CHD-related death and events requiring medical treatment. The goal of this study was to collect a set of studies that represented the state of all scientific literature on omega-3 EPA and DHA supplementation. In addition, studies selected for analysis must have tested for a direct causal relation between the intake of an omega-3 dietary supplement regimen and the relative risk of a CHD event. It was preferred that the selected studies were similar in study protocol in an attempt to control likely variances. Specifically, of the various study methods found for omega-3 fatty acid supplementation, randomized controlled trials (RCT) were preferred because they are designed to directly test for a cause-and-effect relationship between treatment and outcome. Studies were not selected on the basis of the magnitude, direction, or statistical significance of the reported findings.

Overall, 66 studies were found in a PubMed search based on the use of "omega-3" or "polyunsaturated fatty acids"; "coronary heart disease" or "cardiovascular disease"; and "risk reduction" as filtering keywords. The search was conducted between February 1 and May 31, 2013. Ten RCT studies were identified as representative of the literature and were used to deduce the estimated efficacy. All 10 studies were of individuals who had pre-existing CHD or were at high risk of CHD. The treatment groups received omega-3 as a mixture including EPA and DHA—except in one study that administered EPA alone—with dosage rates ranging from 0.6 to 3.4 g of EPA and DHA per day in capsule form. Treatment or placebo was given for various durations across the studies, ranging from 1 to 5 years. Five of the largest studies in terms of subject size are referenced and discussed below, and references for the other five are provided in footnotes to Figure 3.3.

All 10 studies tested for a change in relative risk for CHD events given omega-3 supplementation compared with a control group of no supplementation. Reported primary outcomes usually included total deaths, as well as deaths due to cardiovascular reasons, MI, angina pectoris, intervention by implanted cardioverter/defibrillator, hospital admission due to cardiovascular reasons, stroke, and other specified events. For the purpose of this study, each of these outcomes was considered as a CHD event, as each uses health care services. Hence, the size of the effect, if any, of omega-3 on the incidence of these outcomes can be directly input into the cost model.

To deduce the expected size of a treatment effect on the occurrence of an event, a random-effects literature review approach was adopted based on the literature review process developed by DerSimonian and Laird (D-L approach) (DerSimonian & Laird, Literature Review in clinical trials, 1986). This is an accepted statistical approach for deducing the true treatment effect from a set of clinical/scientific research that varies by sample size, methodologies and study protocols, and patient population dynamics (DerSimonian & Laird, 1986, DerSimonian & Kacker, 2007). This approach allows for a systematic and objective approach to weighing each of the qualified reported effects and combining them to estimate an expected risk reduction factor that can be used to estimate the number of avoided events and avoided expenditures, if a given patient were to use a supplement at a given intake level. An overview of the random-effects model is described in the appendix of this report.

Figure 3.3—Omega-3 Literature Review: Description of the Qualified Studies

Author	Region	Year	Daily dose	Event definition
Tavazzi	Italy	2008	0.85 g of EPA and DHA	Death or hospital admission for cardiovascular reason
Marchioli	Italy	1999	0.85 g of EPA and DHA	Cardiovascular death, non-fatal MI, and non-fatal stroke
Galan	France	2010	0.6 g of EPA and DHA	Cardiovascular death, non-fatal MI, or stroke
Yokoyama	Japan	2007	1.8 g of EPA	Sudden cardiac death, fatal and non-fatal myocardial infarction, and other non-fatal events.
Nilsen[4]	Norway	2001	3.4 g of EPA and DHA	Cardiac death, recurrent MI, resuscitation, unstable angina
Leaf[5]	U.S.	2005	2.6 g of EPA and DHA	Number who experienced primary endpoint by 12 months: death or first ICD intervention
Raitt[6]	U.S.	2005	1.8 g of fish oil	Number who experienced primary endpoint by 24 months
Brouwer[7]	Netherlands	2006	2 g of fish oil	ICD interventions or death from any cause
Svensson[8]	Denmark	2006	1.7 g of EPA and DHA	Acute MI, angina pectoris, stroke, transient ischemic attack, peripheral artery disease requiring surgery, or death
Roncaglioni et al.,	Italy	2013	1.0 gram of EPA and DHA	Time to death from cardiovascular causes or hospital admission for cardiovascular causes

Note: All figures are rounded. Source: Frost & Sullivan

Included in the literature review were the two pinnacle omega-3 studies conducted by the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI). The first key study was the Marchioli et al., (1999) GISSI-Prevenzione trial study, which is a multicenter, open-label, randomized, placebo-controlled trial, with a 2x2 factorial design. This study included 11,324 patients in Italy who were diagnosed with MI three months prior to enrollment, and each group of approximately 2,830 subjects received a daily dose of 0.85 grams of either: (a) omega-3 alone (EPA and DHA); (b) vitamin E (alpha tocopherol) alone; (c) both omega-3 and vitamin E; or (d) placebo. Subjects were followed for an average of 3.5 years. The two primary endpoints were: (A) the cumulative rate of all-cause death, non-fatal myocardial infarction, and non-fatal stroke; and (B) the cumulative rate of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. The study results showed that the two-way analysis of omega-3 versus control demonstrated a relative risk for primary endpoint A of 0.90 (95% CI 0.82 to 0.99) and a relative risk for primary endpoint B of 0.89 (95% CI 0.80–1.01).

4 Nilsen, Albrektsen, Landmark, Moen, Aarsland, & Woie, 2001

5 Leaf, 2006

6 Raitt, et al., 2005

7 Brouwer, et al., 2006

8 Svensson, Schmidt, Jørgensen, & Christensen, 2006

The second GISSI study included in the literature review was the 2008 Tavazzi et al., GISSI-HF trial, which was a designed as a multicenter, randomized, double blind, placebo controlled trial (Tavazzi, 2008). In this study, 6,975 patients in Italy who had chronic heart failure within three months of enrollment were included. Omega-3 EPA and DHA at a daily dose of 0.85 gram per day for the treatment group, as well as a placebo for the control group, was given to the patients, and they were followed for an average of 3.9 years. The two primary endpoints were: (A) time to death; and (B) time to death or admission to hospital for cardiovascular reasons. The results of the study showed that, in comparing the omega-3 group with the placebo group, the hazard ratio for primary outcome A was 0.91 (95.5% CI 0.833–0.998), and for primary outcome B, the hazard ratio was 0.92 (99% CI 0.849–0.999).

Also included in the literature review was the work of Galan et al., 2010 SU.FOL.OM3 trial (Galan, et al., 2003). Designed as a multicenter, double-blind, randomized, placebo-controlled trial with a 2x2 factorial design, 2,501 patients in France with histories of MI, unstable angina, or ischemic stroke were included. Each group of approximately 625 subjects received a daily dose of 0.60 grams of either: (a) omega-3 alone (EPA and DHA); (b) combined vitamins B6 (3 mg), B12 (20 mcg), and folate (560 mcg); (c) both omega-3 and vitamins; or (d) placebo. Subjects were followed for an average of 4.7 years, and the primary endpoint was the first major cardiovascular event, defined as a non-fatal MI, an ischemic stroke, or death from cardiovascular disease. The study results indicated that when comparing omega-3 with the control in a two-way analysis, the hazard ratio for the primary endpoint was 1.08 (95% CI 0.79–1.47).

Another key random control trial included in the literature review was the Yokoyama et al., 2007 JELIS trial (Yokoyama, et al., 2007), which was a multicenter, open-label, blinded, randomized trial with 18,645 subjects in Japan, all of whom were hypercholesterolemic and taking statins. Half of the subjects received a daily dose of 1.8 grams of omega-3 (EPA) and statin, and the other half received statin alone. The subjects were followed for an average of 4.6 years, and the primary endpoint was any major coronary event, including sudden cardiac death, fatal and non-fatal MI, and other non-fatal events, including unstable angina pectoris, angioplasty, stenting, or coronary artery bypass grafting. The results of the study showed that the relative risk for the primary endpoint in the omega-3 group was 0.81 (95% CI 0.69–0.95).

A very recent study considered in this analysis was a multicenter, double- blind, placebo-controlled trial in Italy (Roncaglioni, et al., 2013). The subjects were 12,505 people with multiple cardiovascular risk factors, excluding MI. Half of the subjects received 1 gram per day of omega-3 fatty acids (EPA and DHA) in capsule form, and half received 1 gram of olive oil placebo. Subjects were followed for a median of 5 years, and the primary endpoint was defined as time to death from cardiovascular causes or hospital admission for cardiovascular causes. The results of the study showed that the relative risk for the primary endpoint in the omega-3 group was 0.98 (95% CI 0.88-1.08).

An average of 137,210 avoided events per year from 2013 to 2020 from 2013 to 2020 or 1.1 million accumulated avoided events over the same period if all U.S. adults over the age of 55 diagnosed with CHD were to use omega-3 dietary supplements at preventive intake levels.

Figure 3.4—Omega-3 Literature Review: Description of the Qualified Studies—Summary of Findings

Author	Total sample (N)	% of subjects in treatment group who experienced event (TER)	% of subjects in control group who experienced event (CER)	Relative risk (RR)	Study weight (based on within study and between study variance)
Tavazzi	6,975	56.7%	59.0%	0.96.	17.1%
Marchioli	11,324	9.7%	10.7%	0.90	24.9%
Galan	2,501	6.5%	6.1%	1.06	19.7%
Yokoyama	18,645	2.8%	3.5%	0.81	27.9%
Nilsen	300	28.0%	24.0%	1.17	2.1%
Leaf	402	28.5%	38.6%	0.74	2.5%
Raitt	200	65.0%	59.0%	1.10	1.2%
Brouwer	546	29.7%	33.0%	0.90	3.3%
Svensson	206	60.2%	57.3%	1.05	1.2%
Roncaglioni et al.	12,513	11.7%	11.9%	0.99	20.6%

Note: All figures are rounded. Source: Frost & Sullivan

Empirical Results

Based on the D-L approach of the qualified set of scientific studies outlined in the last section, it is estimated that the relative risk reduction of a CHD event, given the preventive daily use of omega-3 supplements, is 6.9% after controlling for variance because of sample size, research methodologies and study protocols, and patient population differences within each study and among all studies. Further, 133 people needed to be treated with an omega-3 supplement to avoid one CHD event. In other words, if 133 people used omega-3 supplements at an expected protective intake levels of 1,000 mg per day per the recommendation of the American Heart Association[9], one CHD hospitalization event would be avoided. Given an NNT of 133 people, the number of potential avoided events among all U.S. adults over the age of 55 diagnosed with CHD could be an estimated 137,210 avoided events per year from 2013 to 2020, or about 1.1 million cumulative avoided events.

9 (Kris-Etherton, Harris, & Appel, 2002)

Figure 3.5—Omega-3 Literature Review: Summary Results—D-L Approach

Metric	Measure
Weighted relative risk (weighted for intra-study variance) (RR)	93.1%
Weighted relative risk reduction (weighted for intra-study variance) (RRR)	6.9%
Number of people needed to treat to avoid one CHD event (NNT), people	133
Average number of events avoided annually if everybody in the target population* used omega-3, 2013–2020	137,210
Cumulative number of events avoided if everybody in the target population* used omega-3, 2013–2020	1,097,678

*Among all U.S. adults over the age of 55 with CHD
Note: All figures are rounded. Source: Frost & Sullivan

An average annual total hospital utilization cost avoidance of $2.06 billion per year and a cumulative savings of $16.46 billion from 2013 to 2020 is potentially realizable if all U.S. adults over the age of 55 diagnosed with CHD were to use omega-3 dietary supplements at protective intake levels.

Given the same NNT of 133 people, which is achievable if every high-risk person in the target population were to take omega-3 supplements at protective levels daily, the effect on avoided hospital utilization expenditures among all U.S. adults over the age of 55 diagnosed with CHD would be an average avoidance of $2.06 billion per year and a cumulative avoidance of $16.46 billion from 2013 to 2020.

Based on the review of the best-selling retail products currently sold through brick and mortar, online, and mail-order retailers, the price of a daily dose of omega-3 ranges from as low as $0.137 to as high as $0.358 for one gram of EPA and DHA. The median cost of a daily dose of omega-3 is approximately $0.25 per day. Given this daily cost requirement, the median annual expected cost of omega-3 dietary supplementation for all U.S. adults over the age of 55 would be $92.15 per person or $1.57 billion per year for the total subpopulation, and $12.58 billion in cumulative expenditures over the next seven years.

Figure 3.6—Omega-3 Cost Analysis: Summary Results—Cost of Dietary Supplementation of the Target Population*, 2013–2020

Metric	Measure
Median cost of omega-3 supplementation at protective daily intake levels, 2013	$0.25
Expected annual median cost of omega-3 supplementation at protective daily intake levels, 2013	$92.15
Average annual cost of omega-3 dietary supplementation of the target population*, 2013–2020	$1.57 B
Cumulative cost of omega-3 dietary supplementation of the target population*, 2013–2020	$12.58 B

*Among all U.S. adults over the age of 55 with CHD
Note: All figures are rounded. Source: Frost & Sullivan

Nearly $4 billion in cumulative net CHD-attributed cost savings from 2013 to 2020 is potentially realizable if the entire target population were to use omega-3 dietary supplements at protective intake levels.

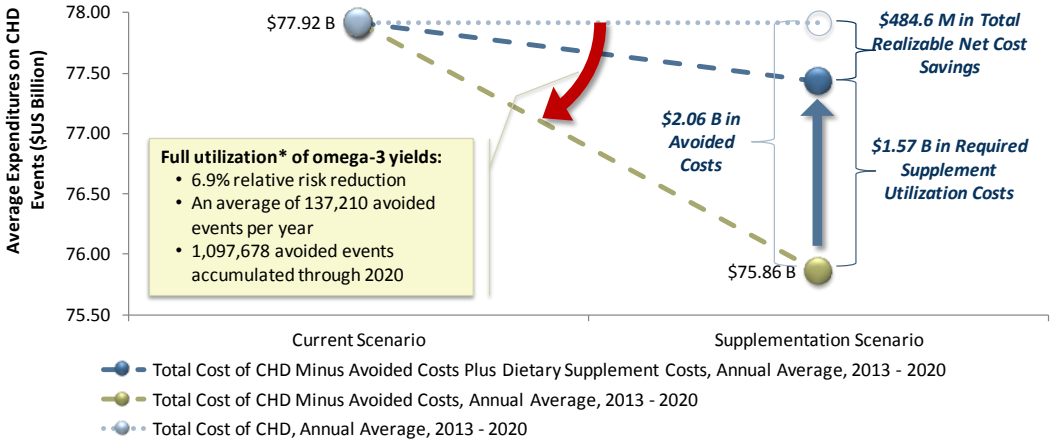
Figure 3.7—Omega-3 Cost Analysis: Summary Results—Avoided Hospital Utilization Expenditures* due to Dietary Supplement Intervention, 2013–2020

Metric	Measure
Average avoided CHD-attributed hospital utilization expenditures given omega-3 supplement intervention per year, 2013–2020	$2.06 B
Cumulative avoided hospital utilization expenditures related to CHD given omega-3 supplement intervention, 2013–2020	$16.46 B
Average annual hospital utilization expenditures for CHD-related events among all U.S. adults over the age of 55 if incidence is reduced through the use of omega-3 supplements, 2013–2020	$75.86 B
Cumulative expenditures on CHD-related events among all U.S. adults over the age of 55 if incidence is reduced through the use of omega-3 supplements, 2013–2020	$606.87 B

*Among all U.S. adults over the age of 55 with CHD
Note: All figures are rounded. Source: Frost & Sullivan

Thus, given that the total cost savings derived from avoided CHD events ($2.06 billion per year—$16.46 billion from 2013 to 2020), the net savings after accounting for the cost of omega-3 dietary supplementation would average $484.6 million per year—more than $3.88 billion in cumulative net savings from 2013 to 2020. See Figures 8.1 to 8.4 in the appendix for detailed reporting of the empirical results.

Figure 3.8—Omega-3 Cost Analysis: Net Health Care Cost Savings* Summary Results, 2013–2020



* Among all U.S. adults over the age of 55 with CHD
Note: All figures are rounded. Source: Frost & Sullivan

Figure 3.9—Omega-3 Cost Analysis: Summary Results—Net Cost Savings* due to Avoided Hospital Utilization Expenditures through Dietary Supplement Intervention, 2013–2020

Metric	Measure
Average net potential direct savings per year from avoided CHD hospital utilization events due to omega-3 dietary supplement intervention, 2013–2020	$484.6 M
Cumulative net potential direct savings from avoided CHD hospital utilization events due to omega-3 dietary supplement intervention, 2013–2020	$3.88 B
Net benefit cost ratio, $ per one dollar spent on dietary supplement	$1.31

*Among all U.S. adults over the age of 55 with CHD
Note: All figures are rounded. Source: Frost & Sullivan

The prior cost-benefit analysis makes the assumption that in the supplementation scenario all U.S. adults over the age of 55 with CHD use omega-3 dietary supplements at preventive daily intake levels from a base of zero usage among this population segment. In other words, the calculated net savings is actually the total potential net savings. However, because a percentage of adults over the age of 55 are known regular users of omega-3 dietary supplements, this target population segment already has a reduced risk of experiencing a costly CHD event and is already realizing omega-3's risk-reducing benefits.

According to the 2012 Council for Responsible Nutrition Consumer Survey on Dietary Supplements conducted by Ipsos Public Affairs, 28% of U.S. adults over the age of 55 are regular users of omega-3/fish oil dietary supplements (Ipsos Public Affairs, 2012)[10]. This implies that the remainder—72%—has yet to realize the potential benefits of the supplements' regular use. Because avoided expenditures and net cost savings are a direct function of the total number of people in the target population using omega-3 dietary supplements, the calculation of avoided health care expenditures and net cost savings yet to be realized is simply a proportional adjustment of the total potential avoided expenditures and net cost savings.

10 It is not known what percentage of this target population also suffers from CHD, but for the purposes of this analysis, Frost & Sullivan has made the assumption that approximately the same percentage (28%) of adults over the age of 55 with CHD also are regular users of omega-3 dietary supplements. Also for the purposes of this analysis, as the Ipsos survey did not ask dosage, Frost & Sullivan has made the assumption that regular users in this target population are highly likely to be consuming enough omega-3 to provide a protective effect. More research is required to test these assumptions.

It is expected that there are significant potential cost savings yet to be realized valued at $2.79 billion in cumulative net CHD-attributed cost savings if all current non-regular users in the high-risk target population were to fully utilize omega-3 dietary supplements among current non-regular users in the high-risk target population.

Knowing this, it is expected that $135.8 million of the $484.6 million in net potential direct savings per year from avoided CHD hospital utilization events because of omega-3 dietary supplement intervention is already realized in total expected CHD costs. Inversely, this equates to an average of nearly 98,000 avoidable events per year yet to be realized due to underutilization of omega-3. This corresponds to an average of $348.8 million per year in net savings yet to be realized due to underutilization of omega-3 dietary supplements—$2.79 billion in cumulative net savings from 2013 to 2020. Thus, it is expected that there are still significant cost savings yet be realized through the increased usage of omega-3 dietary supplements among the high-risk target population.

Figure 3.10—Omega-3 Cost Analysis: Summary Results—Net Cost Savings* Yet to be Realized due to Avoided Hospital Utilization Expenditures through Dietary Supplement Intervention, 2013–2020

Metric	Measure
Percentage of target population* who are regular users of omega-3 dietary supplements, 2012	28.0%
Average number of CHD events avoided annually among the target population* yet to regularly use omega-3, 2013–2020	98,766
Cumulative number of CHD events avoided among the target population yet to regularly use omega-3 , 2013–2020	790,124
Average net direct savings per year from avoided CHD events due to omega-3 dietary supplement intervention yet to be realized, 2013–2020	$348.8 M
Cumulative net direct savings from avoided CHD events due to omega-3 dietary supplement intervention yet to be realized, 2013–2020	$2.79 B

*Among all U.S. adults over the age of 55 with CHD
Note: All figures are rounded. Source: Ipsos Public Affairs and Frost & Sullivan

B Vitamins

Literature Review

Three B vitamins—B6 (pyridoxine), folate (folic acid), and B12 (cyanocobalamin)—have been extensively studied for their roles in cardiovascular health, including CHD (Memorial Sloan-Kettering Cancer Center, 2013).[11] Many foods are natural sources of these vitamins: B6 is inherent in cereals, beans, poultry, fish, and some vegetables and fruits; food folate comes from fruits and vegetables, beans, and whole grains, while folic acid is the form used in fortified foods and dietary supplements; and B12 is derived from poultry, fish, red meat, eggs, and dairy products (Memorial Sloan-Kettering Cancer Center, 2013). The interest in these vitamins in preventing CHD events stems from their role in metabolizing the amino acid homocysteine. The mechanisms connecting homocysteine levels with CHD are unknown, but they may be related to the damaging effects of homocysteine on the vascular endothelium (Memorial Sloan-Kettering Cancer Center, 2013). The analysis in this report is based on studies showing the direct effect on CHD risk, not on homocysteine as a marker of disease risk.

The interest in three B vitamins (B6, folic acid, and B12) that may help reduce CHD events stems from their role in metabolizing the amino acid homocysteine in the blood.

In the United States, the generally recognized recommended daily intake levels for folic acid, B6, and B12 are 400 mcg, approximately 2 mg, and 2.4 mcg, respectively (Harvard School of Public Health Nutrition Source, 2013). However, the clinical research reviewed for this study suggests that the daily intake levels of folic acid, B6, and B12 should be more than 1 mg, 2.5 mg, and 400 mcg, respectively, in order to realize the CHD event-avoiding effects. The upper limit of tolerable intake (UL) for folate is 1000 mcg for all U.S. adults and applies only to intakes of folic acid from fortified foods and dietary supplements. The UL for folic acid is based on the potential for neurological effects in people with B12 deficiency, which is often undiagnosed. (Institute of Medicine, 1998). The UL for vitamin B6 is 100 mg per day for all U.S. adults (Institute of Medicine, 1998). This is based on the potential for neuropathy from very high levels of B6 used for therapeutic purposes such as treatment of carpal tunnel syndrome. No UL was established for B12, and the Institute of Medicine (IOM) report on DRIs for the B vitamins says: "No adverse effects have been associated with excess B12 intake from food or supplements in healthy individuals" (Institute of Medicine, 1998).

11 For the purposes of this study, all references to "B vitamins" refer only to the combination of B6 (pyridoxine), folic acid (folate), and B12 (cyanocobalamin), which are typically marketed together as a homocysteine blocking dietary supplement.

To deduce the effect of B vitamin supplementation on the occurrence of a CHD event, a systematic search was conducted that focused on published studies quantifying the effect of supplementation on the incidence of CHD-related death and events requiring medical treatment. The goal was to collect a set of studies that are representative of the state of scientific understanding of the efficacy of a B vitamin dietary supplement. Studies that tested for a direct causal relation between intake of the dietary supplement and the relative risk of a disease event were preferred, and a concerted effort was adopted to ensure that the down-selected studies were similar in protocol in an attempt to control variance. Studies were not selected on the basis of the magnitude, direction or statistical significance of the reported findings.

A total of 104 studies were found in a PubMed search based on the use of "vitamin B" or "B9" and/or "folic acid" and/or "B12" and/or "B6"; "coronary heart disease," "cardiovascular disease" and related terms, and "risk reduction" as filtering keywords. The search was conducted between February 1 and May 31, 2013. Seven RCT studies were identified as being representative of the literature and included formulations of all three types of B vitamins outlined above. The selected studies directly tested for the relationship between dietary supplement intake and the risk of a CHD-attributed disease event. All seven studies included subjects who had pre-existing cardiovascular disease, such as MI or stroke. The treatment groups received all three B vitamins as a daily supplement, with dosage rates ranging by study but averaging 29 mg (B6), 1.7 mg (folate), and 0.5 mg (B12). The experimental or placebo treatments were given for various durations across the studies, ranging from 1 to 7.3 years. Four of the seven studies are discussed and referenced in the text below, and references for the other three are provided in the footnotes to Figure 3.11.

Figure 3.11—B Vitamins Literature Review: Description of the Qualified Studies

Author	Year	Daily dose (mg)			Event definition
		B6	B12	Folic acid	
Albert	2008	50	1	2.5	First of any of these events: nonfatal myocardial infarction, stroke, coronary revascularization procedures (coronary artery bypass grafting or percutaneous coronary intervention), and cardiovascular mortality
Bonaa[12]	2006	40	0.4	0.8	Composite of recurrent myocardial infarction, stroke, and sudden death attributed to coronary artery disease
Hankey	2010	25	0.5	2	Composite of stroke, myocardial infarction, or vascular death.
Lonn	2006	50	1	2.5	Composite of death from cardiovascular causes, myocardial infarction, and stroke
Toole	2004	25	0.4	2.5	Any stroke, CHD event, or death
Schnyder[13]	2002	10	0.4	1	Composite endpoint of major adverse events defined as death, nonfatal myocardial infarction, and need for repeat revascularization
Galan[14]	2010	3	0.02	0.56	Composite of non-fatal myocardial infarction, stroke, or death from cardiovascular disease

Note: All figures are rounded. Source: Frost & Sullivan

Reported primary outcomes usually included total deaths, death due to cardiovascular reasons, MI, stroke, angina pectoris, coronary revascularization procedures, and other specified events. For the purpose of this study, each of these outcomes was considered as a CHD event because each utilizes health care services. Hence, the size of the effect, if any, of the B vitamins on the incidence of these outcomes can be directly input to the cost model. Six studies reported a relative risk for CHD events comparing B vitamin supplementation with a control group of no supplementation. One study reported the relative risk comparing high-dose with low-dose vitamin supplementation.

Among the seven RCTs analyzed was Albert et al., (2008), the Women's Antioxidant and Folic Acid Cardiovascular Study (WAFACS) trial, which was a randomized, double-blind, placebo-controlled trial that enrolled 5,442 U.S. women who had either a history of CVD or three or more coronary risk factors (Albert, et al., 2008). The active treatment group took a daily combination supplement of 2.5 mg folic acid, 50 mg B6, and 1 mg B12, while the control group took a placebo. The subjects were followed for an average of 7.3 years. The primary outcome measured was a combined endpoint of cardiovascular morbidity and mortality, including MI, stroke, coronary revascularization procedures, and cardiovascular mortality. Analysis showed that the relative risk of the primary outcome in the vitamin group compared with the placebo group was 1.03 (95% CI 0.90 to 1.10).

12 Bønaa, et al., 2006

13 Schnyder, Roffi, Flammer, Pin, & Hess, 2002

14 Galan, Kesse-Guyot, Czernichow, Briancon, Blacher, & Hercberg, 2010

A second study included was that of Hankey et al., (2010), the Vitamins to Prevent Stroke (VITATOPS) trial (Hankey, et al., 2010). This was a multicenter, randomized, double-blind, placebo-controlled clinical trial conducted in 20 countries. Subjects were 8,164 people who had a stroke or transient ischemic attack within seven months of enrollment. Treatment consisted of one tablet daily of placebo or B vitamins (2 mg folic acid, 25 mg B6, and 0.5 mg B12). Subjects were followed for an average of 3.4 years. The primary endpoint was a composite of stroke, myocardial infarction, or vascular death. Analysis of the results showed that the relative risk for the primary endpoint in the vitamin group compared with the placebo group was 0.91 (95% CI 0.82 to 1.00).

Lonn et al., (2006) reported results of the Heart Outcomes Prevention Evaluation-2 (HOPE-2) study (Lonn, et al., 2006). This was designed as a multicenter, randomized, double-blind, placebo-controlled trial. Subjects were 5,522 people recruited in Canada, the U.S., Europe, and Brazil who had a history of vascular disease, or diabetes and additional risk factors. The treatment group took a daily supplement containing 2.5 mg of folic acid, 50 mg B6, and 1 mg B12, while the control group took a placebo. Subjects were followed for an average of five years. The primary study outcome was the composite of death from cardiovascular causes, myocardial infarction, and stroke. In comparing the vitamin group with the placebo group, the relative risk of the primary outcome was 0.95 (95% CI 0.84 to 1.07).

Another large study included in the analysis was that of Toole et al., (2004), the Vitamin Intervention for Stroke Prevention (VISP) trial (Toole, et al., 2004). This was a multicenter, randomized, controlled trial, comparing low and high vitamin doses. In this study, 3,680 people were recruited in the U.S., Canada, and Scotland who had experienced non-disabling ischemic stroke. Treatment was either a daily high vitamin dose (25 mg B6, 0.4 mg B12, and 2.5 mg of folic acid) or low vitamin dose (0.2 mg B6, 0.006 mg B12, and 0.02 mg folic acid). Follow-up was for two years. The primary endpoint was recurrent ischemic stroke, CHD events, or death. Compared with the low-dose group, the relative risk for the primary endpoint in the high-dose group was 0.967 (95% CI 0.8 to 1.1).

Figure 3.12—B Vitamins Literature Review: Description of the Qualified Studies—Summary of Findings

Author	Total sample (N)	% of subjects in treatment group who experienced event (TER)	% of subjects in control group who experienced event (CER)	Relative risk (RR)	Study weight (based on within study and between study variance)
Albert	5,442	14.9%	14.3%	1.04	17.07%
Bonaa	1,880	21.5%	18.2%	1.18	11.23%
Hankey	8,164	15.1%	16.6%	0.91	18.08%
Lonn	5,522	18.8%	19.8%	0.95	16.34%
Toole	3,680	18.0%	18.6%	0.97	14.85%
Schnyder	553	15.4%	22.8%	0.68	5.44%
Galan	2,501	6.0%	6.5%	0.93	16.99%

Note: All figures are rounded. Source: Frost & Sullivan

An average of 101,028 avoided events per year from 2013 to 2020 or 808,225 accumulated avoided events over the same period if all U.S. adults over the age of 55 diagnosed with CHD were to use the B vitamins folic acid, B6, and B12 at protective intake levels.

Empirical Results

Based on the D-L approach, the calculated relative risk reduction of a CHD-related medical event, given the use of B vitamin dietary supplements at preventive daily intake levels, was 3.31%, after controlling for variance because of sample size, research methodologies and study protocols, and patient population differences within each study and among all studies. Following this approach, the calculated NNT is 181 people based on a relative risk reduction of 3.1%. This equates to an average of 101,000 avoided events per year from 2013 to 2020 or 808,000 avoided events cumulatively.

Figure 3.13—B Vitamins Literature Review: Summary Results—D-L Approach

Metric	Measure
Weighted relative risk (weighted for intra-study variance) (RR)	96.7%
Weighted relative risk reduction (weighted for intra-study variance) (RRR)	3.3%
Number of people needed to treat to avoid one CHD event (NNT), people	181
Average annual number of CHD events avoided if everybody in the target population* used B vitamins, 2013–2020, people avoiding events	101,028
Cumulative number of CHD events avoided if everybody in the target population* used B vitamins, 2013–2020, people avoiding events	808,225

*Among all U.S. adults over the age of 55 with CHD
Note: All figures are rounded. Source: Frost & Sullivan

Potential avoided hospital utilization average costs of $1.52 billion per year and a cumulative savings of $12.12 billion from 2013 to 2020 is potentially realizable and avoidable by health care payers if all U.S. adults over the age of 55 diagnosed with CHD were to use B vitamins dietary supplements at protective intake levels.

Given the annual average $16,690 cost per person for a CHD-related event, the potential avoided hospital utilization costs among all U.S. adults over the age of 55 who are also diagnosed with CHD and use B vitamins at protective levels daily, will be on average $1.52 billion per year—a cumulative cost avoidance to health care payers of $12.1 billion from 2013 to 2020.

Based on the review of the best-selling B vitamin supplement products sold as homocysteine blockers through brick- and-mortar, online, and mail-order retail establishments, the price of a daily dose of B vitamins ranges from $0.05 to more than $0.20 for a daily dose. The mean daily cost to consumers is approximately $0.11. Given this $0.11-per-day requirement, the annual expected cost of B vitamins for all U.S. adults over the age of 55 would be slightly more than $50.00 per person, about $861 million per year for the total sub-population, and nearly $6.9 billion in cumulative expenditures from 2013 to 2020.

Knowing that the total cost savings derived from the avoided CHD events for the same population given the use of B vitamins averaged $1.52 billion per year and more than $12.12 billion cumulatively during the forecast period, the net savings, after accounting for the cost of B vitamin dietary supplementation, would be an average of $654.0 million per year and more than $5.23 billion cumulatively. See Figures 7.6 to 7.9 in the appendix for a detailed reporting of the empirical results.

Figure 3.14—B Vitamin Cost Analysis: Summary Results—Cost of Dietary Supplementation of the Target Population, 2013–2020

Metric	Measure
Median cost of B vitamin supplementation at protective levels, 2013	$0.11
Expected annual median cost of B vitamin supplementation at protective levels, 2013	$46.52
Average annual cost of B vitamin dietary supplementation of the target population*, 2013–2020	$861.2 M
Cumulative cost of B vitamin dietary supplementation of the target population*, 2013–2020	$6.89 B

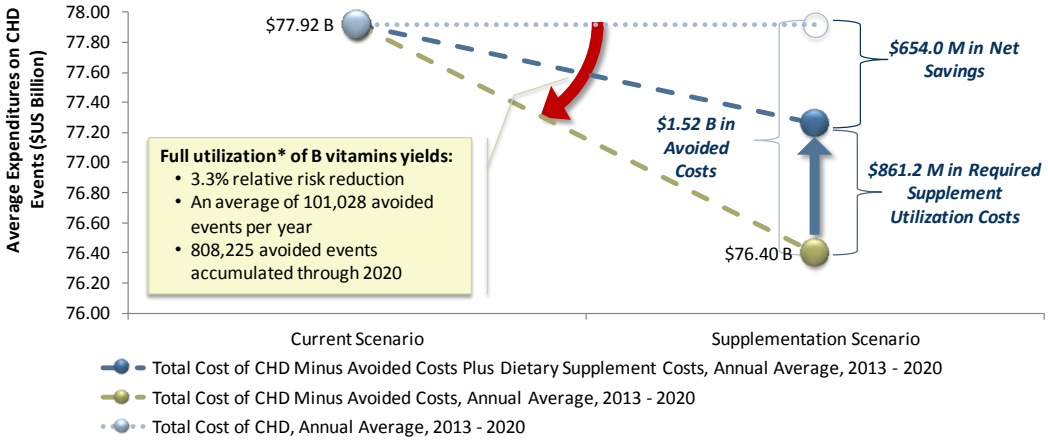
*Among all U.S. adults over the age of 55 with CHD
Note: All figures are rounded. Source: Frost & Sullivan

Figure 3.15—B Vitamins Cost Analysis: Summary Results—Avoided Hospital Utilization Expenditures* due to Dietary Supplement Intervention, 2013–2020

Metric	Measure
Average annual avoided hospital utilization expenditures related to CHD given B vitamin supplement intervention, 2013–2020	$1.52 B
Cumulative avoided hospital utilization expenditures related to CHD given B vitamin supplement intervention, 2013–2020	$12.12 B
Average annual hospital utilization expenditures for CHD-related events if incidence is reduced through the use of B vitamin supplements, 2013–2020	$76.40 B
Cumulative hospital utilization expenditures for CHD-related events if incidence is reduced through the use of B vitamin supplements, 2013–2020	$611.20 B

*Among all U.S. adults over the age of 55 with CHD
Note: All figures are rounded. Source: Frost & Sullivan

Figure 3.16—B Vitamins Cost Analysis: Net Health Care Cost Savings* Summary Results, 2013–2020



* Among all U.S. adults over the age of 55 with CHD
Note: All figures are rounded. Source: Frost & Sullivan

Figure 3.17—B Vitamins Cost Analysis: Summary Results—Net Cost Savings* due to Avoided Hospital Utilization Expenditures through Dietary Supplement Intervention, 2013–2020

Metric	Measure
Average net potential direct savings per year from avoided CHD hospital utilization events due to B vitamin dietary supplement intervention, 2013–2020	$654.0 M
Cumulative net potential direct savings from avoided CHD hospital utilization events due to B vitamin dietary supplement intervention, 2013–2020	$5.23 B
Net benefit cost ratio, $ per one dollar spent on dietary supplement	$1.76

*Among all U.S. adults over the age of 55 with CHD
Note: All figures are rounded. Source: Frost & Sullivan

Over $5 billion in cumulative net CHD-attributed cost savings from 2013 to 2020 is potentially realizable if the entire target population were to use B vitamin dietary supplements at protective intake levels.

It is expected that there are significant potential cost savings yet to be realized valued at nearly $5 billion in cumulative net CHD-attributed cost savings if all current non-regular users in the high-risk target population were to fully utilize B vitamin dietary supplements among current non-regular users in the high-risk target population.

As in the case of the omega-3 dietary supplement cost benefit in the prior section, the B vitamin cost-benefit analysis makes the assumption that in the supplementation scenario all U.S. adults over the age of 55 with CHD use the selected B vitamins at preventive daily intake levels from a base of zero usage among this population segment. In other words, the calculated net savings is the total potential net savings. However, because a significant percentage of adults over the age of 55 are regular users of B vitamin dietary supplements, this segment of the target population already has a reduced risk of a costly CHD event and is realizing its risk-reducing benefits.

According to the 2012 Council for Responsible Nutrition Consumer Survey on Dietary Supplements conducted by Ipsos Public Affairs, 14% of adults over the age of 55 in the United States are regular users of Vitamin B/B Complex dietary supplements (Ipsos Public Affairs, 2012).[15] This implies that 86% have yet to realize the potential benefits of B vitamin dietary supplements' regular use. Because avoided expenditures and net cost savings are a direct function of the total number of people in the target population using B vitamin dietary supplements, it is expected that $92.1 million of the $654.0 million net potential direct savings per year from avoided CHD hospital utilization events is already realized. Inversely, this equates to an average of 86,797 avoidable events per year yet to be realized due to underutilization of B vitamins, which corresponds to an average of $561.8 million per year in net savings yet to be realized—nearly $4.5 billion in cumulative savings from 2013 to 2020. Thus, it is expected that there are significant cost savings yet be realized through the increased usage of B vitamin dietary supplements among the high-risk target population.

15 It is not known what percentage of this target population also suffers from CHD, but for the purposes of this analysis, Frost & Sullivan has made the assumption that approximately the same percentage (14%) of adults over the age of 55 with CHD also are regular users of B vitamin dietary supplements. Also for the purposes of this analysis, as the Ipsos survey did not ask dosage, Frost & Sullivan has made the assumption that regular users in this target population are highly likely to be consuming enough B vitamins to provide a protective effect. More research is required to test these assumptions.

Figure 3.18—B Vitamin Cost Analysis: Summary Results—Net Cost Savings* Yet to be Realized due to Avoided Hospital Utilization Expenditures through Dietary Supplement Intervention, 2012 to 2020

Metric	Measure
Percentage of target population* who are regular users of B vitamin dietary supplements, 2012	14.1%
Average number of events avoided annually among the target population* yet to regularly use B vitamins at protective levels, 2013–2020	86,797
Cumulative number of events avoided among the target population* yet to regularly use B vitamin at protective levels, 2013–2020	694,373
Average net direct savings per year from avoided CHD hospital utilization events due to B vitamin dietary supplement intervention yet to be realized, 2013–2020	$561.8 M
Cumulative net direct savings from avoided CHD hospital utilization events due to B vitamin dietary supplement intervention yet to be realized, 2013–2020	$4.49 B

*Among all U.S. adults over the age of 55 with CHD
Note: All figures are rounded. Source: Ipsos Public Affairs and Frost & Sullivan

Overall, the use of omega-3 and the B vitamins folic acid, B6, and B12 can confer significant potential cost savings for all U.S. adults over the age of 55 with diagnosed CHD if the target population were to use these scientifically substantiated dietary supplements at protective intake levels.

Conclusion

Coronary heart disease (CHD) is the most costly disease in the United States. Use of omega-3 and the B vitamins folic acid, B6, and B12 could result in significant cost savings for adults over the age of 55 with diagnosed CHD if the target population were to use these scientifically substantiated supplements at protective levels.

The net savings potential in avoided costly CHD-related inpatient procedures and emergency room visits because of usage of omega-3 dietary supplements at preventive levels would average nearly $500.0 million per year—a $3.90 billion cumulative health care cost savings from 2013 to 2020. In terms of the ratio of avoided health care costs due to omega-3 supplementation per one dollar spent on omega-3 dietary supplements, $1.31 can be saved per one dollar spent.

Regarding B vitamins, the net savings potential in avoided costly CHD-related inpatient procedures and emergency room visits is more than $650.0 million per year—$5.20 billion cumulatively from 2013 to 2020. In terms of avoided health care costs per one dollar expended on these B vitamins, $1.76 can be saved per $1 spent on B vitamins. These potential health care cost savings are the result of proactively identifying the population that is at greatest risk of experiencing a costly CHD event (adults over the age of 55 with CHD) and helping this population prevent costly events through a dietary supplement regimen. This is a relatively low-technology, yet smart, approach that can be used by consumers, physicians, employers, and policymakers as a means to reduce personal and societal health care costs.