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Smart Prevention—Health Care Cost Savings Resulting from the Targeted Use of Dietary Supplements

An Economic Case for Promoting Increased Intake of Key Dietary Supplements as a Means to Combat Unsustainable Health Care Cost Growth in the United States

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EXECUTIVE SUMMARY

This report demonstrates that the use of specific dietary supplements among those consumers that are at a high risk of experiencing a costly disease-related event can lead to positive health care cost savings.

Project Objectives

The impact of preventive health care on well-being and the potential decrease of total health care expenditures in the United States are strong arguments for the daily use of certain dietary supplements. The objective of this report is to determine the potential net economic savings that could be realized given the usage of dietary supplements that are scientifically shown to reduce the occurrence of disease-related events among targeted population groups. Specifically, this report will attempt to show that using specific dietary supplements by consumers who are determined to be at a high risk of experiencing a costly disease-related event can result in health care cost savings.

A review of dietary supplement scientific literature that covers eight dietary supplement regimens across four non-communicable diseases was carried out. From this review, an overall change in the risk of a given disease-related event with the use of each of the supplements has been deduced. Then, these impact variables are used as a critical input into a cost-benefit scenario analysis to determine the potential change in economic benefits—in terms of avoided hospital utilization costs—that could be realized if everybody in a specified high-risk population group were to use each of the dietary supplements at specified intake levels that have been associated with protective effects. These monetary benefits could be an element in reducing health care costs of vulnerable, high-risk populations, which are the greatest contributors to total health care costs in this country.

The disease conditions and dietary supplement combinations this report examines are:

- Coronary heart disease (CHD) and the potential net health care cost savings when using omega-3 fatty acids, three B vitamins (folic acid, B6, and B12), phytosterols, and psyllium dietary fiber;
- Diabetes-attributed CHD and the potential net health care cost savings when using chromium picolinate;
- Age-related eye disease (ARED), specifically age-related macular degeneration and cataracts, and the potential net health care cost savings when using lutein and zeaxanthin;
- Osteoporosis and the potential net health care cost savings when using the combination of calcium and vitamin D or when using magnesium.

Targeted dietary supplementation regimens are recommended as a means to help control rising societal health care costs and as a means for high-risk individuals to minimize the chance of having to deal with potential costly events and increase quality of life.

Summary of the Findings

This study demonstrates that significant cost savings can be realized by health care payers, such as insurance companies, and consumers through the use of dietary supplements that have a demonstrable and substantial effect on the risk of costly disease-related events among targeted high-risk populations. Specifically, this report will examine evidence showing that the usage of key dietary supplements can reduce overall disease treatment-related hospital utilization costs associated with heart disease, age-related eye disease, diabetes, and bone disease in the United States among those at a high risk of experiencing a costly, disease-related event. Thus, targeted dietary supplementation regimens are recommended as a means to help control rising societal health care costs, and as a means for high-risk individuals to minimize the chance of having to deal with potentially costly events and to invest in increased quality of life.

Regarding CHD, the most costly disease in the United States (Centers for Disease Control and Prevention), this study determined that the use of omega-3 and the B vitamins folic acid, B6, and B12 among all U.S. adults over the age of 55 with diagnosed CHD can confer significant cost savings for health care cost payers given the overall state of knowledge regarding the efficacy of these dietary supplements.

- The potential avoided hospital utilization costs related to CHD through the full utilization of omega-3 supplements at preventive intake levels among the target population can be as much as $2.06 billion on average per year and a cumulative savings of $16.46 billion from 2013 to 2020. The potential net savings in avoided CHD-related hospital utilization costs after accounting for the cost of omega-3 dietary supplements at preventive daily intake levels would be an average of $484.6 million per year, and more than $3.88 billion in cumulative health care cost savings from 2013 to 2020.
- The full utilization of folic acid, B6, and B12 among the target population at preventive intake level's effect on potential avoided CHD-related hospital utilization costs would be an average savings of $1.52 billion per year—a cumulative cost avoidance to health care payers of $12.12 billion from 2013 to 2020. The potential net savings in avoided CHD-related health care costs after accounting for the cost of folic acid, B6, and B12 utilization at preventive daily intake levels would be an average of $654.0 million per year and more than $5.23 billion in cumulative health care cost net savings from 2013 to 2020.

Because scientific evidence generally suggests that the use of phytosterols and psyllium dietary fiber has a direct link in helping to reduce low-density lipoprotein (LDL) cholesterol levels, which, in turn, reduces the risk of experiencing a costly CHD-related event, this study found that realizable cost savings for all U.S. adults over the age of 55 with diagnosed CHD can be significant.

- An average of $4.23 billion per year and a cumulative savings of $34.00 billion from 2013 to 2020 in avoidable hospital utilization costs is potentially realizable if all U.S. adults over the age of 55 diagnosed with CHD were to use phytosterol dietary supplements at protective levels. Likewise, potential total cost savings among the same target population given the use of the psyllium dietary fiber at preventive daily intake levels would be an average hospital utilization cost avoidance of $4.38 billion per year and cumulative savings of $35.05 billion from 2013 to 2020.
- The potential net health care cost savings of phytosterols and psyllium dietary fiber supplementation, after accounting for the cost of supplement utilization, would be an average annual savings of $3.32 billion per year and $2.48 billion per year, respectively, after accounting for the costs of supplementation utilization from 2013 to 2020.

If only the potential avoided hospital utilization costs of type 2 diabetes-attributed CHD events among adults over the age of 55 with diagnosed CHD were considered, avoided expenditures would average $1.22 billion per year—a cumulative savings of $9.75 billion from 2013 to 2020, assuming an annual average cost per person experiencing a CHD-related event of $16,690. This study also determined that the potential net cost savings from avoided CHD events would average $970.0 million per year from 2013 to 2020—nearly $7.76 billion in cumulative savings during the forecast period after accounting for the cost of chromium picolinate dietary supplementation.

In 2012, total direct medical expenditures associated with ARED events (macular degeneration and cataracts) plus the related expected costs of post-procedure nursing care/assisted living services due to reduced vision were almost $16.97 billion and are expected to average $20.55 billion per year from 2013 to 2020. Based on the deduced eye health benefit from using lutein and zeaxanthin dietary supplements, if every person over the age of 55 with ARED were to take lutein and zeaxanthin supplements at the preventive daily intake levels, avoidable expenditures related to AMD would average $57.4 million per year from 2013 to 2020. In addition, the effect on avoided direct medical costs and post-procedure assisted living costs related to cataracts given the daily use of lutein and zeaxanthin supplements at preventive levels would average $3.81 billion per year. This study further determined that an average of $966.6 million per year in net avoided medical costs and nearly $7.73 billion in cumulative net savings from 2013 to 2020 could be realized after accounting for the cost of dietary supplement intervention.

Osteoporosis is the most prevalent bone disease in the United States, accounting for more than $14.00 billion in direct health care costs in 2012 because of fractures. Given complete utilization of calcium and vitamin D supplements by all U.S. women over the age of 55 diagnosed with osteoporosis at preventive daily intake levels, an average of $1.87 billion per year and a cumulative savings of $15.00 billion from 2013 to 2020 in avoidable hospital utilization costs are potentially realizable. Moreover, more than $1.52 billion in net health care cost savings—$12.15 billion over the next seven years—could be realized after accounting for the cost of dietary supplementation. Magnesium dietary supplement intake could result in an average of $851.0 million per year and $6.80 billion cumulatively from 2013 to 2020 in avoidable hospital utilization costs if all U.S. women over the age of 55 diagnosed with osteoporosis were to use magnesium dietary supplements at preventive intake levels. Furthermore, net health care cost savings of $595.3 million per year and more than $4.76 billion cumulatively over the next seven years is potentially realizable after accounting for the cost of dietary supplementation.

BACKGROUND

Approximately 75% of total U.S. health care expenditures are spent on preventable diseases but only 3% of total health care expenditures are invested in disease prevention programs.

Problem Statement

A common question among policymakers, public health experts, and consumers that is, in many ways, still unaddressed is whether health care costs can be avoided if more preventive measures are adopted. On the surface, it seems that the answer would be a logical yes, in that preventing diseases is a better option than having to pay for costly treatments. According to the Centers for Disease Control and Prevention (CDC), approximately three quarters of total U.S. health care expenditures are spent on preventable diseases, including such conditions as coronary heart disease, diabetes, age-related eye disease, and osteoporosis (Centers for Disease Control and Prevention), but only 3% of health care expenditures are invested in disease prevention programs (American Public Health Association - Center for Public Health Policy, 2012).

Although the U.S. health care system today does not have as strong an emphasis on preventive medicine as other Western countries, many observers predict that the United States is in the midst of a slow revolution of its health care model—transitioning to a model that is more focused on maintaining individual and overall health and wellness as opposed to a continued reactive approach focused on single-event interventions. However, a deeper look into the cost-effectiveness of prevention reveals many variables that must be accounted for—including which diseases are preventable, the efficacy of the proposed preventive measures, and, ultimately, the relative cost—before an informed decision on the optimal distribution of health resources by policymakers, public health experts, and consumers can be made.

Some observers question investing more money and effort into preventive health and wellness programs, citing two key issues that may make prevention less cost-effective than one would expect (Cohen, Neumann, & Weinstein, 2008) (Russell, 2007). The first issue is that the most well-known prevention practices, such as regular physician checkups or healthy people participating in more laboratory-based procedures (including cancer screenings and blood work), do not actually improve one's health. However, this is also not prevention in the true sense of the word; rather, it is a form of health diagnostics, and diagnostics do not prevent illness. Instead, they identify illnesses for possible utilization of costly acute treatment services. The second issue is that prevention realizes relatively little net cost savings because of the large number of people who would need to adopt preventive measures to avoid just one costly disease-attributed event. However, this argument ignores the core definition of prevention, which is a set of activities that an individual adopts to help minimize his or her chance of experiencing an undesired disease-attributed event.

The adoption of a prevention regimen can help mitigate possible damage to an individual's health and wellness, as well as possible financial impacts that could occur if the individual develops a preventable disease.

Proponents state that true prevention implies a lifelong habit of adopting lifestyle practices that are known to favor better health. These include paying attention to diet and weight, adopting an active lifestyle, and avoiding risky behaviors such as smoking and drinking alcohol. The use of certain dietary supplements may also help delay or prevent certain diseases. The objective of prevention is to improve health throughout life—in the growing years, during reproduction, and while aging. Improved health can also be expected to result in lower health care costs, especially in those life stages (such as older adults and seniors) when costs are most likely to occur. Specifically, the adoption of a prevention regimen helps to mitigate potential damage to an individual's health and wellness, as well as financial effects that could occur, if the individual develops a disease.

Despite the uncertainty surrounding the cost-effectiveness of prevention, its role as a component in overall health and wellness is gaining traction. Most Americans are aware of the challenges facing the country's health care system: escalating costs, denied tests and treatments, fragmented care, less time available for a patient-physician relationship, medical errors and inefficiencies, and other problems. However, important cultural, technological, and demographic trends are increasingly putting more control into the hands of patients to directly manage their health. This transformation has enormous potential to change how medicine is practiced and how the health care system, as a whole, operates.

This shift is directly driven by the need to look for smarter ways to control the escalating costs associated with rising disease-incidence rates for preventable diseases—or, at a minimum, to identify high-risk populations and minimize their chances of experiencing costly events. There are many ways to address rising costs, including the use of new technologies that identify high-risk populations before they experience costly acute treatment events; the adoption of a new health care model that incentivizes consumers, health care professionals, and other key stakeholders to address the antecedents of disease as opposed to the utilization of acute treatment services; and increased education. A low-technology, yet smart, approach that could be more extensively used by consumers and physicians might feature certain dietary supplements that have been scientifically shown to help reduce the risk of experiencing a costly disease event among high-risk population groups.

In the United States, dietary supplements are defined by the Dietary Supplement Health and Education Act (DSHEA) of 1994 as products that are orally ingested and contain nutrients or other dietary components meant to supplement the diet (U.S. Food and Drug Administration, 2013). Dietary supplements come in many forms, including tablets, capsules, liquids, powders, and more. Nutritional components of dietary supplements include vitamins, minerals, fatty acids, proteins, and amino acids (U.S. Food and Drug Administration, 2013). A significant amount of scientific research has been conducted involving dietary supplements, and many studies demonstrate that these supplements have a positive effect on reducing the risk of a disease event. Disease events require costly treatments, but there have been few efforts to calculate the cost-effectiveness of such dietary supplement use.

There is a need for an objective and systematic assessment of the current state of scientific findings regarding the link between the use of dietary supplements and the reduction in the risk of a disease that requires costly treatment services. Understanding this link will help key stakeholders—including patients, physicians, governments, and private insurance companies and employers—make recommendations on the best course of action to help minimize current and future costs and maximize benefits. This report examines the potential health care cost savings if people over the age of 55 use certain dietary supplements that have been shown to lower disease risks. Specifically, this report will examine evidence that demonstrates that the use of key dietary supplement ingredients can reduce illness-related hospital utilization costs associated with heart disease, age-related eye disease, diabetes, and bone disease in the United States.

A significant amount of scientific research has been conducted involving dietary supplements, and many studies demonstrate that these supplements have a positive effect on reducing the risk of a disease event.

If an event risk reduction can be determined and applied into a cost-benefit model, then this will help patients, health care professionals, governments, insurance companies, and employers determine whether a given treatment regimen is cost-effective.

Research Methodology

This report presents a cost-benefit analysis (CBA) comparing the effect on overall disease management costs if a high-risk population were identified and if that population were to increase its use of dietary supplements and incur the cost of such supplementation, with the expectation that supplement use would decrease each person's odds of experiencing a costly treatment event. CBA can be used to assess various cost scenarios and to identify the potential savings or loss that can be realized if one scenario occurred versus another.

This analysis is centered on a series of hypothetical scenarios for a set of common dietary supplements to determine whether a net savings can be realized in the costs of disease management services if costly medical events are avoided through the use of a specific dietary supplement compared with scenarios of no supplement usage. Net savings will suggest a strong economic argument for each person in a given high-risk population to use the given dietary supplement to reduce lifetime disease management costs.

This issue is similar to many that pharmacoeconomic/clinical studies aim to address, which is the determination of an overall treatment's effect on the outcome of a given event when a treatment regimen is applied to one group versus a control group. From these types of analyses, risk—and subsequently risk reduction of an event occurring—can be calculated and applied into a cost-benefit model that helps key decision makers (including patients, health care professionals, governments, insurance companies, and employers) determine whether a treatment is cost-effective.

To deduce the true effect of treatment with a given dietary supplement on the occurrence of a specific disease event, a rigorous search was conducted focusing on published studies that quantified the effect of dietary supplementation on the incidence of disease events that required direct medical treatment. The goal was to collect a set of studies that represented the overall state of understanding and general acceptance on the level of efficacy a given dietary supplement has on affecting the relative risk of a disease event occurrence.

Basically, a thorough review of scientific evidence that shows a likely effect of the intake of each key dietary supplement on the occurrence of chronic, disease-related events was undertaken. This intervention effect can be quantified into a risk reduction metric, which can be included in a cost-benefit model for scenario assessment. The process of deriving the risk reduction metric for each key dietary supplement followed the same overarching, rigorous process of identifying the relevant and representative scientific studies that show an effect on disease event occurrence through a rigorous search exercise and deducing an overarching measure of relative risk between dietary supplement users versus nonusers. Specifically, Frost & Sullivan took the following steps to derive the expected risk reduction metrics for use in the cost savings model:

Review of the scientific literature related to the given chronic disease and the dietary supplement

Frost & Sullivan first instigated a rigorous scientific literature search and built a database of key studies that investigated a causal relationship between supplement intake and the incidence of specific health conditions of interest. Studies were included in the database. Scientific studies included in the database include case studies, observational epidemiologic studies, and clinical trials adhering to best practice scientific methodologies and inclusion was independent of whether the findings were positive, negative, or null. The search exercise used the U.S. National Library of Medicine's PubMed database. All studies reviewed were retrieved between February 1 and May 31, 2013. More than 400 studies were identified based on the use of a strict set of keyword combinations including the dietary supplement of interest, the disease of interest, and the words "risk reduction" or similar phrasing.

Identification of a representative set of qualified studies that investigated a causal relationship between supplement intake and the incidence of specific health conditions of interest

Once the database of possible studies was created, each study was thoroughly reviewed and assessed to determine whether there was a quantifiable relationship between supplement intake and the incidence of a specific chronic disease event, either directly or indirectly through a specified biomarker. Specifically, a study was considered qualified for inclusion in the analysis if it tested for a relationship between the intake of a given dietary supplement at a specific dosage level range and the reduction in the odds of a disease event occurring, independent of the direction of the relationship.[1] Typically, observational epidemiologic studies and randomized clinical trials fit this criterion. If such studies were not found, then studies were reviewed that tested for causal relationship between supplement intake and the level of a biomarker that is correlated to the relative risk of a disease event. Frost & Sullivan strove to include studies that were similar in study protocol in an attempt to control for observable variance. In addition, the research team strove for the ideal of exhaustive inclusion of all studies, but that cannot be guaranteed because of time and resource constraints. Frost & Sullivan makes no claims of endorsing the specific findings of any scientific study reviewed.

1 The selection of studies included in this analysis was not based on the direction, the magnitude, or statistical significance of the reported findings.

Weighting and aggregation of the qualified study findings in order to determine an overall expected impact of dietary supplement intervention on disease event occurrence

In any cost-benefit analysis, there is a need to identify a variable that reflects the effect that the activity will have on overall costs and benefits. Only then can one undertake a comparative analysis between two scenarios. Economists refer to this as output elasticity, which is a ratio that shows a change in a specified output given a change in a specified input. Frost & Sullivan searched for scientific studies that showed a direct relationship between the usage of a specific dietary supplement and the risk of experiencing a defined disease-attributed hospitalization event or a biological marker, such as LDL cholesterol levels and hemoglobin A1c (HbA1c) levels, which can be linked to the chance of a disease-attributed event.

To deduce an estimate on these output elasticities, each qualified study result was weighted by the precision of its findings to derive an overall expected risk reduction (RR) metric. For this study, two approaches were used to derive the expected effect of dietary supplement intervention on disease event occurrence. The specific approach adopted per dietary supplement type was dependent on the quantity of the qualified studies that explore the relationship between intake and disease event risk and the nature of the collective literature.

The DerSimonian and Laird random-effects literature review approach (D-L approach) was used in cases where a dietary supplement had a significant number of scientific/clinical studies that directly explored the specific question that this study aims to address (DerSimonian & Laird, Literature Review in clinical trials, 1986). The D-L approach allows one to properly assess the results of a set of studies that address the same research question, even though each study varies in terms of sample size, study protocol, research team, and a host of other study qualities. This variance is addressed by controlling for inter-study and intra-study variance, and provides a more probable and exact estimate of the overall effect of intervention (see Appendix for details on the D-L approach methodology and details on the calculation of relative risk (RR) and relative risk reduction (RRR) metrics.

In cases where the D-L random-effects literature review approach is not appropriate, such as the case when the number of qualified studies is small or when the relationship between the supplement intervention's impact and the utilization of costly treatment services is indirect, the Center for Evidence-Based Medicine (CEBM) approach was adopted to calculate the number of people needed to treat in order to avoid one major disease event (Center for Evidence Based Medicine, 2012). In these cases, all that is needed for the calculation is an estimate of the relative risk reduction and the observed event rate (ER) or the observed disease prevalence in the target population. It should be noted that the estimated number needed to treat is less accurate compared to the D-L approach and consequently the calculated estimate tends to be inflated. Thus, the determined cost saving estimates will be less precise compared to the cost savings calculated using the D-L approach but still provide invaluable insight of the given supplement's potential cost savings and health care cost effectiveness (see Appendix for details on the CEBM methodology and details on the calculation of relative risk reduction (RRR)).

Health care cost savings scenario analysis

Independent of which literature review approach was used, the key metric needed for inclusion in the cost models is the number needed to treat (NNT), which can easily be calculated using the deduced RRR metrics from the literature review. The NNT is the total number of people who would have to undergo a preventive or treatment intervention to realize one avoided undesired event. This metric was selected as the variable of focus in this study because it is easy to associate an expected health care cost per person experiencing an event. For example, if it was found that a given dietary supplement had an NNT of 100, this would mean that 100 people would need to be supplemented to avoid one major disease event in the target population.

Once the NNT for a given dietary supplement regimen is known, the number of possible avoided events that could be realized if everybody in a given population were to use the supplement at an adequate or protective daily intake level can be calculated; knowing the cost per event, the total avoided costs can be estimated. For example, consider the case of omega-3. It is known that 17.0 million adults over the age of 55 have documented CHD and that 4.8 million people in this group will experience a new CHD event in 2012. Thus, if the total population had used omega-3 at preventive daily intake levels, 127,601 CHD hospital utilization events would have been avoided based on the deduction from current scientific literature that the expected relative risk reduction in experiencing a costly CHD event is 6.9%. This implies an NNT metric of 133 people who needed to be treated to avoid one event (refer to Figure 3.5 for the detailed description of the derived relative risk metric for omega-3 intake). Given that the cost of each CHD event averaged $13,317 in 2012, the potential avoided hospital utilization costs would have been approximately $1.7 billion in 2012.

In order to have realized this total cost savings potential, then all 16.6 million adults over the age of 55 with CHD would have had to take omega-3 at preventive daily levels at a total subpopulation supplement utilization cost of $1.57 billion. Thus, the net benefit that could have been gained would have been more than $131.0 million in avoided CHD-related hospitalization costs in 2012.

Figure 2.1—Summary of Cost Calculations Assuming Omega-3 and Coronary Heart Disease Cost Hypothetical Case, 2012

Reference column	Metric	Measure	Note
A	Target population with CHD, 2012*	17,016,536	Source: CDC and Frost & Sullivan
B	Expected number of people within the target population who will experience a CHD hospitalization event, 2012	4,831,679	Source: MEPS and Frost & Sullivan
C	NNT (from literature review)	133	Source: Frost & Sullivan
D	Expected annual cost of CHD hospital utilization per person, 2012	$13,316.66	Source: MEPS
E	Annual cost of omega-3 dietary supplementation per person, 2012	$92.15	Source: Frost & Sullivan
F	Number of events avoided if everybody in the target population took a supplement, 2012	127,601	A/C = F
G	Avoided hospital utilization costs, 2012	$1,699,224,829	D*F = G
H	Costs of omega-3 supplementation, 2012	$1,568,065,776	A*E = H
I	Net cost savings, 2012	$131,159,053	G - H = I

* Among all U.S. adults over the age of 55 with CHD
Source: Frost & Sullivan

Thus, once the expected risk reduction factor is derived from the literature review, the potential cost savings derived from dietary supplement usage among a given high-risk population at preventive daily intake levels can be calculated and compared with the extreme scenario of zero usage. The calculation of total cost savings is straightforward:

- Total expenditure on chronic disease events at zero usage
- **MINUS** total expenditure on chronic disease events given the use of dietary supplements at protective levels and the expected reduction in chronic disease events because of reduced risk
- **PLUS** the dietary supplement utilization costs
- **EQUALS** potential net cost savings derived from the lower occurrence of disease events because of increased dietary supplement usage

Thus, if the possible net cost savings is positive, then the dietary supplement regimen in question should be considered an effective means to help reduce overall disease-related individual lifetime costs and total social health care costs. Of course, the prior cost-benefit analysis approach makes the assumption that in the supplementation scenario, the entire population of the target high-risk population must fully utilize the given dietary supplements at protective intake levels from a base of zero use among this same population segment. In other words, the calculated net savings is actually the total potential net savings that are realizable. However, because it is known that it is likely that a percentage of the target high-risk population is already regularly using the dietary supplement in question, this share of the target population has already reduced its risk of experiencing a costly disease event and is already realizing its risk-reducing benefits.

If the possible net cost savings is significantly positive, then the dietary supplement regimen in question should be considered as an effective means to reduce overall disease-related individual lifetime costs and total social costs as a whole.

Logically, this also implies that the remainder of the potential regular users has yet to realize the potential preventive benefits from regular use of the given dietary supplements. Because avoided expenditures and net cost savings are a direct function of the total number of people in the target population using the 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. These yet-to-be-realized adjustments are also calculated in each of the scenario analyses conducted in this study and are reflected in their respective chapters.

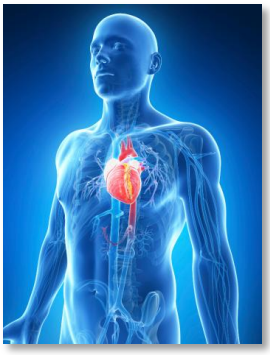
Research Limitations and Assumptions

It should be noted that each dietary supplement explored in this study was analyzed independently, and cross-comparisons should be avoided. This is basically because the state of the science today does not support this approach; event risk for each supplement was examined in a controlled setting, independent of the use of other supplements. The definition of disease-attributed events and the associated per-person costs of treatment vary by disease condition; thus, derived benefits and costs are not comparable across disease conditions. Also, benefits of different supplements (such as omega-3 fatty acids and B vitamins) in reducing the risk of a single disease (such as CHD) cannot be considered to be additive. In addition, variance because of study sample size, research methodologies and study protocols, and patient population characteristics within each study and among all studies is high, making cross-comparison of dietary supplements unadvisable.

However, there is enough evidence from this report's findings that suggest that the net cost savings realizable were people to take a set or a combination of dietary supplements is highly likely to be greater than just using one of the dietary supplements. Certainly, more research would be required to substantiate this statement and determine if cost savings is accumulative (the sum of the savings), synergistic (the sum of the savings is higher than the net savings from using a combination of supplements due to offsetting effects/redundancies in the mechanism of action), or antagonistic (the sum of the savings is lower than the net savings from using a combination of supplements). Frost & Sullivan makes no claims of endorsing the specific findings of any scientific study reviewed.

Regarding cost estimate forecasts, expected compound annual growth rates were derived from a historic assessment of population growth rates, costs, and prices. Specifically, health care costs per person are expected to grow at an average annual growth rate of 5% from 2013 to 2020 based on the historical growth rate over the last 10 years. This growth rate was applied for all procedures for all conditions assessed in this study. Growth in the targeted population is expected to occur at an average annual growth rate of 1.7% during the forecast period, and it was assumed that growth in disease incidence is equal to population growth based on a review of population growth and disease incidence trends. Dietary supplement retail prices are expected to grow at a compound annual growth rate of 1% per year. All future expenditures on health care costs and dietary supplements were at a 3% discount rate, which is in line with health economic methods promoted by the World Health Organization to reflect the present value of estimated future expenditures and net savings and control for inflationary effects (World Health Organization, 2008).

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.

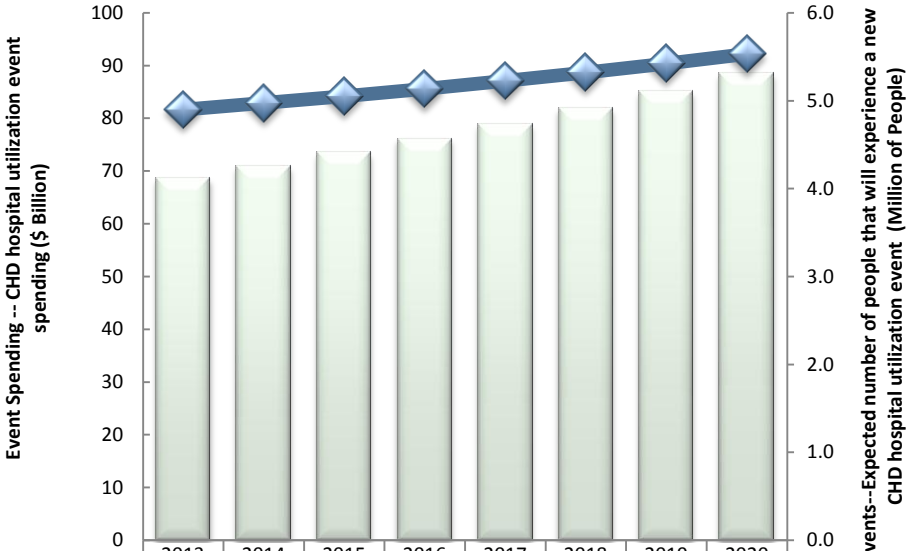
Prevalence and Social Consequences

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.

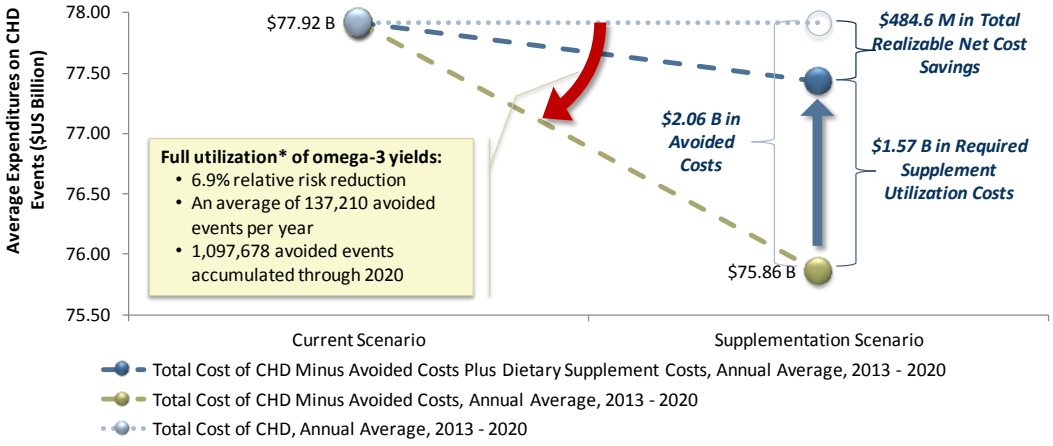
Figure 3.7—Omega-3 Cost Analysis: Summary Results—Avoided Hospital Utilization Expenditures* due to Dietary Supplement Intervention, 2013–2020

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

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.

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.

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

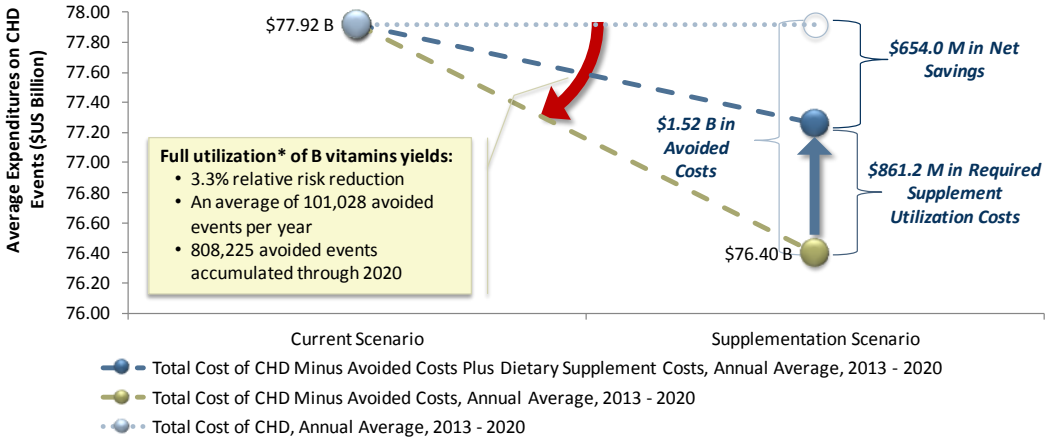
*Among all U.S. adults over the age of 55 with CHD
Note: All figures are rounded. Source: Frost & Sullivan

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.

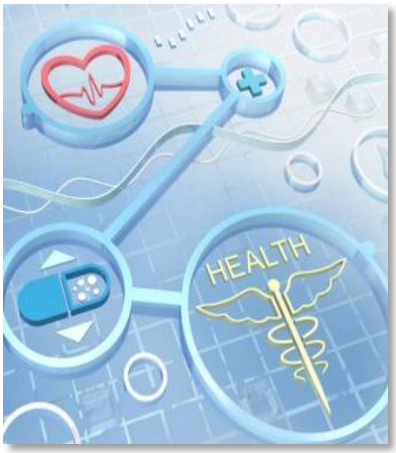
Conclusion

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.

LDL-CHOLESTEROL REDUCTION AND CHD-COST SAVINGS THROUGH PHYTOSTEROL AND PSYLLIUM DIETARY FIBER USAGE



Reducing an individual's LDL cholesterol level will help to reduce his or her odds of experiencing a costly CHD event.

Prevalence and Social Consequences

Hypercholesterolemia is defined as the occurrence of higher concentrations of low-density lipoprotein (LDL) cholesterol and lower concentrations of functional HDL cholesterol, which is correlated to a higher risk of coronary heart disease because of the promotion of plaque development in arteries. Basically, when too much LDL cholesterol accumulates in arteries, it can cause blockage and increase the risk of a heart attack or stroke (American Heart Association, 2012). According to the CDC, more than 13% of all U.S. adults have high cholesterol (Centers for Disease Control and Prevention, 2012). Over the last several decades, progress has been made in dyslipidemia treatment in both increased awareness and treatment development. Current treatment guidelines dictate that LDL cholesterol should be the primary target of therapy.

It is expected that any intervention, including dietary supplementation, that is shown to reduce a person's LDL cholesterol level will also help to reduce the odds of experiencing a costly CHD event. According to the National Institutes of Health, it is estimated that a 1% reduction in LDL-cholesterol level, on average, reduces risk for hard CHD events (myocardial infarction and CHD death) by approximately 1% (Grundy, et al., 2004). Furthermore, according to research conducted by the Cholesterol Treatment Trialists' (CTT) Collaboration in 2010, the risk reduction of a major vascular event (coronary death, MI, coronary revascularization, or stroke) was 15% to 22% per year, given an LDL reduction of 0.51 mmol/L to 1.07 mmol/L (Baigent, et al., 2010). This corresponds to a mean risk reduction of 28% to 21% per 1.0 mmol/L reduction in LDL, or a relative risk reduction of 0.74% to 1.56% given a 1 mg/dL reduction in LDL-cholesterol levels. Thus, Frost & Sullivan deduces that a 1.2 mg/dL reduction in serum LDL-cholesterol reduces the risk of CHD by 1% (Baigent, et al., 2010).

In this chapter, a review of the scientific literature related to phytosterol and psyllium dietary fiber intake and its possible effect on reducing LDL cholesterol levels is provided. This CEBM approach-based literature review is used to determine the expected effect on reducing the chance of experiencing a costly CHD event, and the possible net cost saving is calculated.

The consumption of phytosterols, which are structurally related to cholesterol found in animals, has been shown to help hinder cholesterol absorption in the digestive tract.

Phytosterols

Literature Review

Plants contain compounds called phytosterols that are structurally related to cholesterol found in animals (Cleveland Clinic, 2011). Phytosterols are present in high concentrations in vegetable oils and nuts, although other plant sources contribute to their total dietary intake. There are many distinct phytosterols, of which beta-sitosterol and campesterol are among the most abundant. Normal dietary intake of phytosterols ranges from 0.15 to 0.45 g per day (Ostlund, 2002). Phytosterol consumption has been known to lower cholesterol levels, and evidence points to a mechanism in which phytosterols hinder cholesterol absorption in the digestive tract. Because of the connection to reducing cholesterol levels, the FDA allows health claims for consumption of phytosterols as part of a diet that may reduce the risk of heart disease. The National Cholesterol Education Programs (NCEP) recommends that the daily intake for phytosterols—at levels that confer a CHD event avoidance benefit through cholesterol reduction—is 2 g per day (Cleveland Clinic, 2011).

To quantify the possible effect of phytosterol consumption on the occurrence of a CHD event, a rigorous search was conducted that focused on identifying published studies quantifying the effect of phytosterol supplementation on blood levels of LDL cholesterol. The goal was to collect a set of studies that were representative of the state of scientific literature known today regarding phytosterol's efficacy. First, the team searched for studies that tested for a direct causal relationship between intake of the dietary supplement and the relative risk of a disease event was conducted, but none were identified. Thus, the research team reviewed studies that tested for a causal relationship between supplement intake and the level of a biomarker, which is correlated to the relative risk of a disease event. The research team sought to include studies that were similar in terms of study and methodology protocol to control observable variance. Studies were not selected on the basis of the magnitude or direction or statistical significance of the reported findings.

In all, 42 studies matched keyword combinations such as "phytosterol"; "coronary heart disease" or "cardiovascular disease"; and "risk reduction." The search was conducted between February 1 and March 31, 2013. Of the reported study methods, randomized controlled trials (including sequential and crossover studies) were preferred because they are designed to directly test for a cause-and-effect relationship between supplementation and outcome. Nine RCT studies were identified as being representative of the literature. The included studies indirectly tested for the relationship between dietary supplement intake and the risk of a CHD-attributed disease event through the LDL-cholesterol biomarker.

All nine studies included subjects who had hypercholesterolemia. The RCTs compared a treatment group that received daily phytosterol supplement with a placebo group. In the sequential studies, all subjects received daily phytosterol supplement for a period either before or after a period taking only placebo. In the crossover studies, the subjects took either phytosterols or placebo for a period, followed by a washout period; then, they switched to the opposite product. In all studies, phytosterol supplementation or placebo was given for 2 to 6 weeks, depending on the study. Four of the studies are referenced and discussed in the text below, and references are given for the other five in the footnotes to Figure 4.1.

Figure 4.1—Phytosterols Literature Review: Description of the Qualified Studies

Author	Year	Event definition		Study description and primary event outcome
		Sterol ester	Free sterol equivalent	
Acuff	2007	1.3 g	0.8 g	Study Type - RCT; Population - Hyper-cholesterol-emic; Outcome - Plasma LDL
Maki et al.,	2012		1.8 g	Study Type - RCT; Population - Hyper-cholesterol-emic; Outcome - Plasma LDL
McPherson[16]	2005		1.26 g	Study Type - RCT; Population - ; Outcome - LDL-cholesterol
Lau	2005		1.8 g	Study Type - RCT; Population - Type 2 diabetic, and non-diabetic; Outcome - LDL-cholesterol
Carr	2009	3.0 g		Study Type - RCT; Population - Normal adults; Outcome - LDL-cholesterol
De Graaf[17]	2002		1.8 g	Study Type - RCT; Population - Hyper-cholesterol-emic; Outcome - Plasma total cholesterol
Hallikainen[18]	2002		2.0 g	Study Type - Treatment only; Population - Mildly hyper-cholesterol-emic; Outcome - Serum LDL cholesterol
Mussner[19]	2002		1.82 g	Study Type - RCT; Population - Mildly hyper-cholesterol-emic; Outcome - Total cholesterol
Nestel[20]	2001		2.4 g	Study Type - RCT; Population - Hyper-cholesterol-emic; Outcome - LDL-cholesterol

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

16 McPherson, Ostlund, Goldberg, Bateman, Schimmoeller, & CA, 2005

17 De Graaf, et al., 2002

18 Hallikainen, Sarkkinen, Wester, & Uusitupa, 2002

19 Mussner, Parhofer, Von Bergmann, Schwandt, Broedl, & Otto, 2002

20 Nestel, Cehun, Pomeroy, Abbey, & Weldon, 2001

Among the nine studies analyzed was that of Maki et al., (2012) (Maki et al., 2012). This was a randomized, crossover study that enrolled 32 U.S. subjects who were hypercholesterolemic. The subjects first received a placebo for five weeks, followed by either placebo or phytosterol for six weeks, and then crossed over to the opposite product for six weeks. Phytosterol was given as 1.8 g per day in tablet form. Plasma lipid profiles were measured at the end of each treatment period. The analysis showed that compared with the placebo, the average LDL-cholesterol concentration after six weeks of phytosterol supplementation decreased by a statistically significant 4.9%, equivalent to an average reduction of 7.6 mg/dL (0.19 mmol/L).

Another study analyzed was that of Carr et al., (2009) which was a randomized, parallel, placebo-controlled study that enrolled 32 U.S. subjects, 24 of whom were hypercholesterolemic, while the remainder were normocholesterolemic (Carr, Krogstrand, Schlegel, & Fernandez, 2009). Each day for four weeks, the subjects took either 3 g of phytosterol (in ester form) or a placebo. Plasma lipid profiles were measured at the end of the treatment period. Analysis showed that, compared with the placebo group, the average LDL-cholesterol concentration after four weeks of phytosterol supplementation decreased by a statistically significant 11%, equivalent to a reduction of 16 mg/dL (0.41 mmol/L).

Acuff et al., (2007) conducted a placebo-controlled sequential study on 16 U.S. subjects who were hypercholesterolemic, with a four-week placebo phase followed by a two-week washout period, and then a four-week treatment phase (Acuff, Cai, Dong, & Bell, 2007). Phytosterol (in ester form) was given as a capsule at a dose of 1.3 g per day, equivalent to 0.8 g per day of free phytosterol. At the end of the treatment period, LDL cholesterol in the phytosterol group decreased on average by a statistically significant 4% (6.1 mg/dL, 0.16 mmol/L) compared with the placebo group.

Lau et al., (2005) studied phytosterol supplementation in a randomized, crossover, placebo-controlled trial in Canada that consisted of two 21-day treatment (placebo or supplement) periods that were separated by a 28-day washout period (Lau, Journoud, & Jones, 2005). Twenty hypercholesterolemic subjects took part, 15 of whom were diabetic. Phytosterols were given as 1.8 g per day mixed with margarine and served on toast. An analysis of lipid profiles at the end of the treatment periods showed that for the non-diabetic subjects, LDL cholesterol was reduced by an average of 15.1% (24 mg/dL, 0.62 mmol/L) after phytosterol compared with placebo consumption. For diabetic subjects, the reduction in LDL was 26.8%.

Figure 4.2—Phytosterols Literature Review: Description of the Qualified Studies—Summary of Findings

Author	Total sample (N)	Change in LDL cholesterol mg/dL (absolute outcome reduction)	Change in LDL cholesterol mmol/L (absolute outcome reduction)	Study weights (based on sample size variance)
Acuff	16	6.1	0.1576	6.2%
Maki	32	7.6	0.1970	12.5%
McPherson	52	10.4	0.2687	20.2%
Lau	29	24.4	0.6300	5.4%
Carr	32	16.3	0.4200	6.2%
De Graaf	70	19.0	0.4900	12.1%
Hallikainen	11	18.2	0.4700	4.3%
Mussner	63	10.0	0.2584	24.5%
Nestel	22	25.2	0.6500	8.6%
Average	29	13.4*	0.3935*	

* Weighted Average

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

An average of 283,389 events per year could be avoided from 2013 to 2020, which is nearly 2.3 million accumulated avoided events over the same period if all U.S. adults over the age of 55 diagnosed with CHD were to use phytosterol dietary supplements at protective levels.

Empirical Results

The research team had to deduce the level of phytosterol's efficacy through an assessment of its effect on a relevant biomarker known to have a casual relationship with a given subject's relative risk of experiencing a CHD event. Specifically, reported study outcomes included plasma or serum concentrations of LDL cholesterol and other lipids before, during, and at the end of the treatment or placebo periods. The research team linked these outcomes to health care utilization based on evidence that the observed reduction in LDL cholesterol would decrease the risk of CHD. Thus, the research team derived the expected CHD risk reduction metric given the reduction in LDL cholesterol levels based on the work of the Cholesterol Treatment Trialists' (CTT) Collaboration in 2010, where a 1.2 mg/dL reduction in serum LDL-cholesterol reduces the risk of CHD by 1% (Baigent, et al., 2010).

Thus, the expected relative risk reduction of a CHD-related medical event, given the use of phytosterol dietary supplements at preventive daily intake levels among the target population, was 11.2% based on the review of the scientific literature. This expected risk reduction metric assumes a 1% reduction in relative risk for every 1.2 mg/dL reduction in LDL cholesterol levels. To calculate the NNT, an event rate of 16% was used because this is the expected level of risk of a CHD event among the adult population over the age of 55 (National Health and Nutrition Examination Survey, 2013). Using the CEBM approach (Center for Evidence Based Medicine, 2012) to calculate NNT, this implies that the total number of people who must be treated with phytosterols to avoid one CHD event is 65. In other words, if 65 people adopted a phytosterols regimen at protective levels as a means to reduce their LDL cholesterol levels, one avoided CHD event could be realized. Given this calculated NNT, an annual average of 283,389 avoided events from 2013 to 2020 and 2,267,111 cumulative avoided events over that period could be expected.

An average of $4.23 billion per year and a cumulative savings of $34.00 billion from 2013 to 2020 in avoidable hospital utilization costs is potentially realizable if all U.S. adults over the age of 55 diagnosed with CHD were to use phytosterol dietary supplements at protective levels.

Figure 4.3—Phytosterols Literature Review: Summary Results—CEBM Approach

Metric	Measure
Weighted relative risk reduction (weighted for sample size variance) (RRR)	11.2%
CHD event rate (ER)	16%
Number of people needed to treat to avoid one CHD event (NNT), people	65
Average number of events avoided annually if everybody in the target population* used phytosterols at protective levels, 2013–2020, people	283,389
Cumulative number of events avoided if everybody in the target population* used phytosterols at protective levels, 2013–2020, people	2,267,111

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

Using the same annual average cost per person for a CHD-related event ($16,690), the total potentially avoidable hospital utilization cost for all U.S. adults over the age of 55 diagnosed with CHD given the use of the phytosterols at preventive daily intake levels would average $4.2 billion per year—a cumulative total savings of $34.0 billion from 2013 to 2020 to health care cost payers.

A review of retail products on the market showed that the consumer cost of a daily dose (2 grams) of phytosterols is roughly $0.15. The annual expected cost of phytosterols for the target population would average slightly more than $54.48 per person, for a total of $872.7 million per year—a cumulative cost of nearly $7.0 billion in supplement expenditures from 2013 to 2020.

Based on the finding that the total cost savings derived from avoided CHD events for the target population given the use of phytosterols was, on average, $4.2 billion (nearly $34.0 billion cumulatively during the forecast period), the net cost savings derived from the daily use of phytosterols, after accounting for the cost of supplementation, would average $3.3 billion per year—nearly $26.6 billion cumulatively. In terms of the calculated cost-benefit ratio, $4.87 in avoided health care expenditures could be realized per $1 spent on phytosterol supplementation. See Figures 8.9 to 8.12 in the appendix for a detailed reporting of the empirical results.

Figure 4.4—Phytosterols Cost Analysis: Summary Results—Cost of Dietary Supplementation of the Target Population, 2013–2020

Metric	Measure
Median cost of phytosterol supplementation at protective levels, 2013	$0.15
Expected annual median cost of phytosterol supplementation at protective levels, 2013	$54.48
Average annual cost of phytosterol dietary supplementation of the target population*, 2013–2020	$872.7 M
Cumulative cost of phytosterol dietary supplementation of the target population* , 2013–2020	$6.98 B

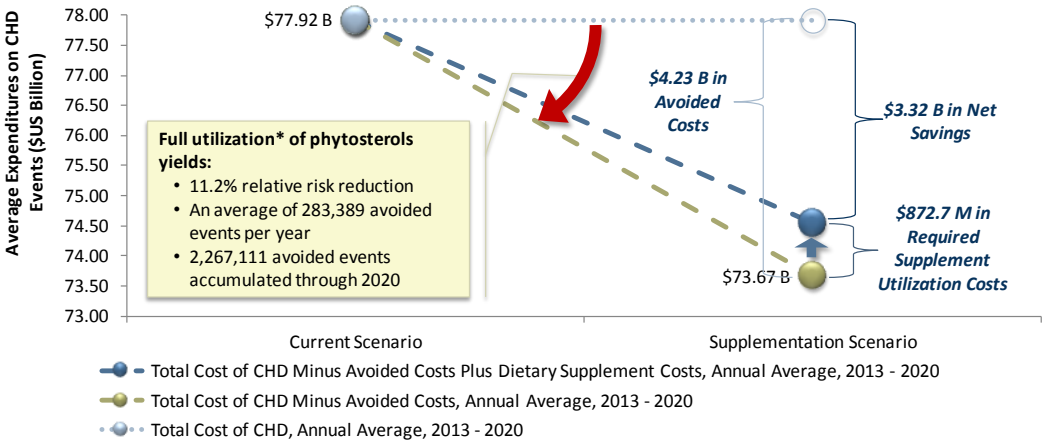
*Among all U.S. adults over the age of 55 with CHD
Note: All figures are rounded. Source: Frost & Sullivan

Figure 4.5—Phytosterols 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 if incidence is reduced through phytosterol supplements, 2013–2020	$4.23 B
Cumulative avoided hospital utilization expenditures related to CHD if incidence is reduced through phytosterol supplements, 2013–2020	$34.00 B
Average annual hospital utilization expenditures for CHD-related events if incidence is reduced through phytosterol supplements, 2013–2020	$73.67 B
Cumulative expenditures on CHD-related events if incidence is reduced though phytosterol supplements, 2013–2020	$589.33 B

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

Figure 4.6—Phytosterols 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 4.7—Phytosterols 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 phytosterol dietary supplement intervention, 2013–2020	$3.32 B
Cumulative net potential direct savings from avoided CHD hospital utilization events due to phytosterol dietary supplement intervention, 2013–2020	$26.56 B
Net benefit cost ratio, $ per one dollar spent on dietary supplement	$4.87

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

$26.56 billion in cumulative net CHD-attributed cost savings from 2013 to 2020 is potentially realizable if the entire target population were to use phytosterol dietary supplements at protective intake levels.

It is expected that less than 0.2% of adults over the age of 55 are already regular users of phytosterol dietary supplements, suggesting that nearly all of the potential net cost health care savings have yet to be realized.

This cost-benefit analysis makes the assumption that in the supplementation scenario all U.S. adults over the age of 55 with CHD use phytosterol/stanols supplements at protective 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, only 0.2% of adults over the age of 55 are regular users of phytosterol dietary supplements, according to the 2012 Council for Responsible Nutrition Consumer Survey on Dietary Supplements conducted by Ipsos Public Affairs. (Ipsos Public Affairs, 2012).[21] This suggests that nearly all of the expected $3.3 billion in potential net savings has yet to be realized, thus, it is expected that there are significant cost savings yet be realized through the increased usage of phytosterol dietary supplements among the high-risk target population.

Figure 4.8—Phytosterols 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 adults over the age of 55 who are regular users of phytosterol dietary supplements, 2012	0.15%
Average number of CHD events avoided annually among the target population* yet to regularly use phytosterol, 2013–2020	282,950
Cumulative number of CHD events avoided among the target population* yet to regularly use phytosterol, 2013–2020	2,263,602
Average net direct savings per year from avoided CHD hospital utilization events due to phytosterol dietary supplement intervention yet to be realized, 2013–2020	$3.31 B
Cumulative net direct savings from avoided CHD hospital utilization events due to phytosterol dietary supplement intervention yet to be realized, 2013–2020	$26.52 B

*Among all U.S. adults over the age of 55 with CHD

Source: Note: All figures are rounded. Source: Ipsos Public Affairs and Frost & Sullivan

21 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 (0.2%) of adults over the age of 55 with CHD also are regular users of phytosterol 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 phytosterol to provide a protective effect. More research is required to test these assumptions.

Psyllium Dietary Fiber

Psyllium dietary fiber has been found to help lower cholesterol by inhibiting cholesterol absorption in the intestine.

Literature Review

Dietary fiber includes soluble and insoluble fiber from plant foods. The composition of fiber depends on its source. The type and amount of fiber consumed has many effects on the physiology of digestion. For example, the intestinal absorption of bile acids, along with the cholesterol that they carry, is slowed by the presence of soluble fiber in the intestine. Certain soluble fibers, such as beta-glucans and arabinoxylans, are more effective at lowering cholesterol than other types of fiber.

Psyllium dietary fiber, for example, is a common soluble fiber and has traditionally been used as a gentle bulk forming laxative (University of Maryland Medical Center, 2013). Sourced from the Plantago ovata herb, psyllium dietary fiber is most commonly grown in India and its husks have been found to help lower cholesterol (University of Maryland Medical Center, 2013).

The Institute of Medicine (IOM) of the National Academy of Sciences (NAS) recommends that women consume 25 g of dietary fiber per day and men consume 38 g per day based on an optimal diet formula stating that at least 14 g of fiber is needed for every 1,000 calories (Institute of Medicine, 2006). There is no established UL for total fiber. According to the IOM report, "[a]lthough occasional adverse gastrointestinal symptoms are observed when consuming some of the isolated or synthetic fibers, serious chronic adverse effects have not been observed. A UL was not set for dietary fiber or functional fiber. Because of the bulky nature of fibers, excess consumption is likely to be self-limited" (Institute of Medicine, 2006).

As in the case of the phytosterols analysis, a rigorous search was conducted that focused on identifying published studies quantifying the effect of psyllium dietary fiber supplementation on blood levels of LDL cholesterol. The objective was to identify a set of studies that represented the state of scientific literature on the subject of psyllium dietary fiber and its link to CHD risk. In this analysis, studies that were reviewed tested for a causal relationship between psyllium dietary fiber intake and the level of a biomarker that is correlated to the relative risk of a disease event because no studies that tested for the direct relationship were identified. The research team included only studies similar in methodology protocol in an attempt to control for observable variance. Studies were not selected on the basis of the magnitude, direction or statistical significance of the reported findings.

Specifically, 102 studies matched the keyword combinations of "fiber"; "coronary heart disease" or "cardiovascular disease"; and "risk reduction." The search was conducted between February 1 and March 31, 2013. The preferred studies were randomized, controlled trials. For the sake of closer comparison, the research team sought to analyze studies using the same type of fiber supplement. Four RCT studies were identified as being representative of the literature on psyllium dietary fiber. The included studies indirectly tested for the relationship between psyllium fiber intake and the risk of a CHD-attributed disease event through the LDL-cholesterol biomarker. The four RCTs tested psyllium fiber supplementation in hypercholesterolemic individuals. In all studies, the supplement was consumed for between 40 days and 26 weeks, and the blood lipids (including LDL cholesterol) were measured and compared for treatment and control subjects.

Figure 4.9—Psyllium Dietary Fiber Literature Review: Description of the Qualified Studies

Author	Year	Daily treatment dose (g)	Study description
Anderson	2000	10.2	Study Type - RCT; Population - Hyper-cholesterolemic; Fiber Supplement Type—Psyllium
Anderson	1991	10.2	Study Type - RCT; Population - Hyper-cholesterolemic; Fiber Supplement Type—Psyllium
Anderson	1999	10.2	Study Type - RCT; Population - Diabetic and Hyper-cholesterolemic; Fiber Supplement Type—Psyllium
Everson	1992	15.0	Study Type - RCT; Population - Hyper-cholesterolemic; Fiber Supplement Type—Psyllium

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

Anderson et al., (1991) studied 52 hypercholesterolemic U.S. subjects (Anderson, Floore, Geil, O'Neal, & Balm, 1991). All subjects first completed a cholesterol-lowering diet over a period of eight weeks. They maintained the diet while they were randomly assigned to supplement with either psyllium fiber (10.2 g/day) or placebo. After eight weeks of consuming the supplement, LDL cholesterol levels of the psyllium group had declined by 17 mg/dL (0.45 mmol/L) compared with the placebo, a statistically significant difference.

Everson et al., (1992) studied 20 U.S. men with mild hypercholesterolemia (Everson, Daggy, McKinley, & Story, 1992). In a randomized crossover design, the subjects received a 40-day course of psyllium fiber supplement (15 g/day) or placebo, followed a washout period of 11 days, and then crossed over to the other treatment. The psyllium fiber treatment resulted in a significant 10 mg/dL (0.26 mmol/L) decrease in LDL cholesterol compared with the placebo.

In a study of 29 U.S. men who had both hypercholesterolemia and diabetes, Anderson et al., (1999) randomly assigned either psyllium (10.2 g/day) or a placebo after a two-week period of dietary stabilization (Anderson, Allgood, Turner, Oeltgen, & Daggy, 1999). After eight weeks of treatment, serum lipids and other markers were measured. Relative to the placebo group, the LDL-cholesterol concentration in the psyllium group had declined by an average of 17.8 mg/dL (0.46 mmol/L). The difference did not achieve significance.

Finally, in a multicenter study in the U.S., Anderson et al., (2000) recruited 248 subjects with hypercholesterolemia (Anderson, et al., 2000). Subjects were put on a cholesterol-lowering diet for an initial eight-week period, and then randomly assigned to receive psyllium fiber or a placebo supplement. After 26 weeks, the average LDL-cholesterol concentration declined by 10.4 mg/dL (0.27 mmol/L) in the psyllium group compared with the placebo group. The difference was statistically significant.

Figure 4.10—Psyllium Dietary Fiber Literature Review: Description of the Qualified Studies—Summary of Findings

Author	Total sample (N)	Change in LDL cholesterol mg/dL (absolute outcome reduction)	Change in LDL cholesterol mmol/L (absolute outcome reduction)	Study weights based on sample size variance
Anderson	248	10.45	0.2700	76.4%
Anderson	52	17.42	0.4500	10.1%
Anderson	29	17.80	0.4600	5.8%
Everson	40**	10.00	0.2584	7.8%
Average	92	13.9	0.3596	

* Weighted Average
**Crossover study

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

Empirical Results

Because the set of qualified studies examined the link between the use of psyllium fiber and the reduction in LDL cholesterol, the research team followed the same approach as the one adopted for the phytosterol literature review and assumed that 1.2 mg/dL reduction in serum LDL cholesterol reduces the risk of CHD by 1% based on the work of the CTT Collaboration (Baigent, et al., 2010). The research team then indirectly arrived at a relative risk of CHD from dietary fiber supplementation to apply to its economic analysis.

The expected relative risk reduction of a CHD-related medical event, given the daily use of psyllium dietary fiber at preventive daily intake levels among all people over the age of 55 diagnosed with CHD, was 11.5%. As in the phytosterol analysis, an event rate of 16% was adopted because 16% of the adult population over the age of 55 is at a high risk of experiencing a CHD-related event. Using the CEBM approach to calculate NNT, this suggests that 63 people need to be treated with psyllium dietary fiber to avoid one CHD event. Given this deduced NNT, an annual average of 292,165 avoided events from 2013 to 2020—2,337,318 cumulative avoided events could be realized.

An average of 292,165 avoided events per year from 2013 to 2020 or over 2.3 million accumulated avoided events over the same period if all U.S. adults over the age of 55 diagnosed with CHD were to use psyllium dietary fiber at protective intake levels.

Figure 4.11—Psyllium Dietary Fiber Literature Review: Summary Results—CEBM Approach

Metric	Measure
Weighted relative risk reduction (weighted for inter-study variance) (RRR)	11.5%
Event rate (ER)	16%
Number of people needed to treat to avoid one CHD event (NNT), people	63
Average number of CHD events avoided annually if everybody in the target population* used phytosterols, 2013–2020, people	292,165
Cumulative number of CHD events avoided if everybody in the target population* used phytosterols, 2013–2020, people	2,337,318

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

In terms of avoided direct health care expenditure, a potential total cost savings among all U.S. adults over the age of 55 diagnosed with CHD given the use of the psyllium dietary fiber at preventive daily intake levels would be an average annual total savings of $4.2 billion per year and cumulative savings of $34.0 billion from 2013 to 2020, assuming an annual average cost per person experiencing a CHD-related event at $16,690.

Based on the reviewed studies, all patients underwent a preliminary dietary program to help standardize daily intakes of dietary fiber and other macro- and micronutrient intake levels, in order to help control for that possible variance. Thus, all patients in the psyllium fiber treatment groups are assumed to have been consuming comparable levels of dietary fiber prior to treatment. In addition, the U.S. Food and Drug Administration allows companies to claim on their product labels that intake of 7 g or more per day of psyllium soluble fiber may reduce the risk of CHD (U.S. Food & Drug Administration, 2012). Based on the qualified studies, the expected dose size for psyllium fiber was in the range of 10.2 to 15.0 g of psyllium fiber per day. For the purposes of this study, Frost & Sullivan assumed a conservative daily dose of psyllium fiber of 10 g was sufficient to realize its expected health-conferring benefits.

Based on the review of best-selling psyllium dietary fiber retail products in brick-and-mortar, online, and mail-order retail establishments, the cost of a daily dose of 10 g of psyllium dietary fiber is just over $0.30 per day. Based on this cost, the annual expected cost of psyllium fiber for all U.S. adults over the age of 55 would be just over $111.31 per person—more than $1.9 billion per year on average for the total sub-population, and more than $15.2 billion cumulatively from 2013 to 2020.

Figure 4.12—Psyllium Dietary Fiber Cost Analysis: Summary Results—Cost of Dietary Supplementation of the Target Population*, 2013–2020

Metric	Measure
Median cost of psyllium dietary fiber at protective levels, 2013	$0.30
Expected annual median cost of psyllium dietary fiber at protective levels, 2013	$111.31
Average annual cost of psyllium dietary fiber supplementation of the target population*, 2013–2020	$1.90 B
Cumulative cost of psyllium dietary fiber supplementation of the target population*, 2013–2020	$15.20 B

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

Figure 4.13—Psyllium Dietary Fiber 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 if incidence is reduced through the use of psyllium dietary fiber, 2013–2020	$4.38 B
Cumulative avoided hospital utilization expenditures related to CHD if incidence is reduced through the use of psyllium dietary fiber, 2013–2020	$35.05 B
Average annual hospital utilization expenditures for CHD-related events among all U.S. adults over the age of 55 if incidence of events is reduced though the use of psyllium dietary fiber, 2013–2020	$73.53 B
Cumulative hospital utilization expenditures for CHD-related events among all U.S. adults over the age of 55 if incidence of events is reduced though the use of psyllium dietary fiber, 2013–2020	$588.28 B

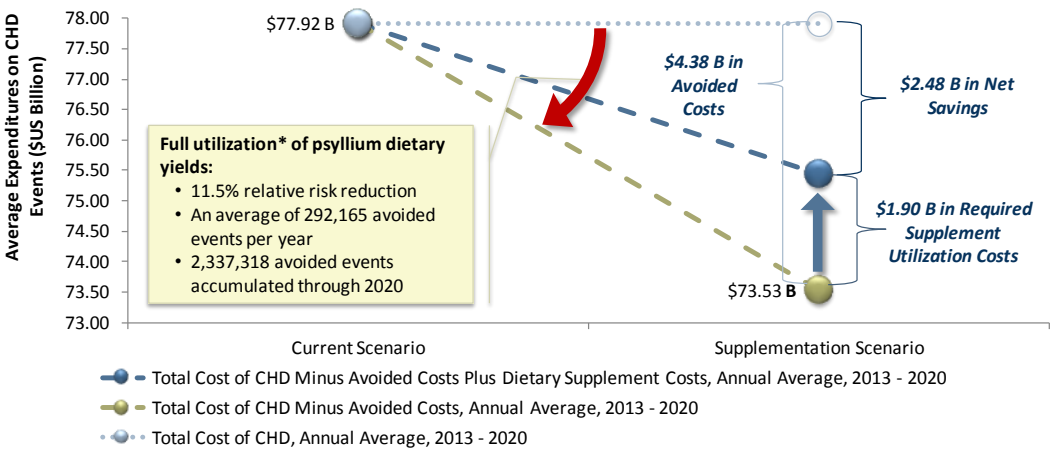
*Among all U.S. adults over the age of 55 with CHD
Note: All figures are rounded. Source: Frost & Sullivan

Given the total cost savings derived from avoided CHD events for the target population based on the use of psyllium dietary fibers, the net savings in direct expenditures after accounting for the cost of psyllium dietary fiber supplementation would average $2.5 billion per year, and more than $19.9 billion cumulatively from 2013 to 2020. In terms of the calculated cost benefit ratio, $2.31 in avoided health care expenditures could be realized per $1 spent on psyllium dietary fiber supplementation. See Figures 8.13 to 8.16 in the Appendix for a detailed reporting of the empirical results.

An average annual total savings of $4.38 billion per year and a cumulative savings of $35.05 billion from 2013 to 2020 is potentially realizable if all U.S. adults over the age of 55 diagnosed with CHD were to use protective levels of psyllium fiber.

Nearly $20 billion in cumulative net CHD-attributed cost savings from 2013 to 2020 is potentially realizable if the entire target population were to use psyllium dietary fiber at protective levels.

Figure 4.14—Psyllium Dietary Fiber 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 4.15—Psyllium Dietary Fiber 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 if incidence is reduced through the use of psyllium dietary fiber, 2013–2020	$2.48 B
Cumulative net potential direct savings from avoided CHD hospital utilization events if incidence is reduced through the use of psyllium dietary fiber, 2013–2020	$19.85 B
Net benefit cost ratio, $ per one dollar spent on dietary supplement	$2.31

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

This cost-benefit analysis assumes that in the supplementation scenario all U.S. adults over the age of 55 with CHD used psyllium dietary fiber at protective 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 share of adults over the age of 55 regular use psyllium dietary fiber, this segment of the target population already has a reduced risk of experiencing a costly CHD event and is already realizing its risk-reducing benefits.

According to the 2012 Council for Responsible Nutrition Consumer Survey on Dietary Supplements conducted by Ipsos Public Affairs, 8% of adults over the age of 55 in the United States are regular users of fiber supplements (Ipsos Public Affairs, 2012).[22] This implies that the remainder—92%—has yet to realize the benefits of regular use of dietary fiber, including psyllium fiber. Because avoided expenditures and net cost savings are a direct function of the total number of people in the target population using psyllium dietary fiber, 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.

Knowing this, it is expected that $199.6 million of the $2.48 billion in net potential direct savings per year from avoided CHD hospital utilization events because of psyllium dietary fiber intervention is already realized in the total expected CHD costs. This equates to an average of 268,647 avoidable events per year yet to be realized because of underutilization of psyllium dietary fiber. This corresponds to an average of $2.28 million per year in net savings yet to be realized because of underutilization of psyllium dietary fiber—nearly $18.25 billion in cumulative net savings from 2013 to 2020. Thus, it is expected that there are significant cost savings yet be realized through the increased usage of psyllium dietary fiber among the high-risk target population.

It is expected that there are significant potential cost savings yet to be realized valued at nearly $18 billion in cumulative net CHD-attributed cost savings if all current non-regular users in the high-risk target population were to fully utilize psyllium dietary fiber.

Figure 4.16—Psyllium Dietary Fiber 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 psyllium dietary fiber, 2012	8.0%
Average number of CHD hospital utilization events avoided annually among the target population* yet to regularly use psyllium dietary fiber, 2013–2020	268,647
Cumulative number of CHD hospital utilization events avoided among the target population* yet to regularly use psyllium dietary fiber, 2013–2020	2,149,175
Average net direct savings per year from avoided CHD hospital utilization events due to psyllium dietary fiber intervention yet to be realized, 2013–2020	$2.28 B
Cumulative net direct savings from avoided CHD hospital utilization events due to psyllium dietary fiber intervention yet to be realized, 2013–2020	$18.25 B

* Among all U.S. adults over the age of 55 with CHD

Source: Note: All figures are rounded. Source: Ipsos Public Affairs and Frost & Sullivan

22 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 (8%) of adults over the age of 55 with CHD also are regular users of fiber dietary supplements. The Ipsos survey did not ask specifically about the type of fiber supplements being taken. Even in the unlikely event that all the fiber supplements were psyllium products, that would leave 92% of the population yet to achieve the benefit of psyllium fiber supplementation. 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 fiber to provide a protective effect. More research is required to test these assumptions.

There are significant health care cost savings to be realized if there was a concerted effort to identify high CHD risk populations and motivate them to adopt a dietary supplement regime as a means to help control escalating costs associated with preventable disease events.

Conclusion

Phytosterols and psyllium dietary fiber could confer significant potential cost savings for all U.S. adults over the age of 55 with diagnosed CHD. A significant amount of scientific research has already been conducted involving phytosterols and psyllium dietary fiber, and there is an indication that these supplements produce a likely positive impact on disease risk reduction. However, more scientific research should be undertaken to test this hypothesis in order to avoid the use of indirect means to calculate the expected number needed to be treated to avoid one CHD event. The potential cost saving derived from the use of phytosterol and psyllium dietary fiber supplements at preventive daily intake levels is expected to be significant because of the direct link to lowering LDL cholesterol levels. It is because of this direct link that the postulation was made that there would be consequential impact on reducing the risk of experiencing a CHD event.

Overall and independent of the exact figures calculated in this analysis, what has been demonstrated in this analysis is that there are likely significant health care cost savings to be realized through a concerted effort to identify high CHD risk populations and motivate them to use phytosterol and psyllium dietary fiber supplements as a means to help control escalating social costs associated with rising disease-incidence rates for preventable diseases. There are many ways to identify and motivate high CHD risk people to use effective dietary supplements, including the use of new technologies that identify high-risk populations before they experience costly acute treatment events; the use of incentives for consumers, health care professionals, and other key stakeholders to address the antecedents of disease as opposed to the utilization of acute treatment services; and increased general education. Only then can a smarter approach that utilizes certain dietary supplements that have been shown scientifically to help reduce the risk of experiencing a costly disease event among high disease-risk population groups be effective at controlling potential health care costs.

THE USE OF CHROMIUM PICOLINATE AND ITS EFFECT ON THE RISK OF DIABETES-ATTRIBUTED CORONARY HEART DISEASE

The total health care expenditure on managing and treating diabetes-attributed CHD among diabetics over the age of 55 with CHD will be an average of $33 billion per year from 2013 to 2020.

Prevalence and Social Consequences

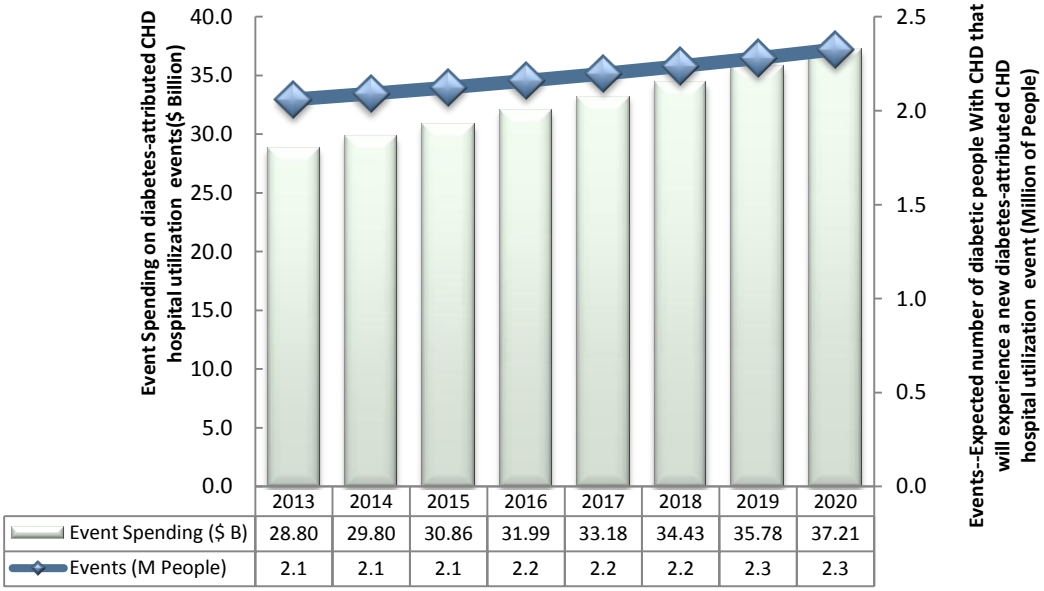
Type 2 diabetes mellitus (type 2 diabetes) is the most common form of diabetes in the United States; 90 to 95% of diabetes patients suffer from type 2 diabetes. The total health care cost of diabetes in 2012 in the United States was about $245 billion, of which $176 billion was attributed to direct medical costs and $69 billion in reduced productivity, according to the American Diabetes Association (American Diabetes Association, 2011). Regarding direct medical costs, nearly 60% of total expenditures are related to hospitalizations. Type 2 diabetes is a chronic disease marked by high levels of glucose in the blood. It is most common in patients that are over the age of 55, have a high-density lipoprotein (HDL) cholesterol of less than 35 mg/dL or triglyceride level of greater than 250 mg/dL, and/or have high blood pressure. The primary means to inhibit complications related to type 2 diabetes are diet and exercise. However, if diet and exercise do not help a person maintain normal glucose levels, physicians may have to prescribe medication.

In 2012, it was estimated that more than 17 million U.S. adults over the age of 55 suffered from diabetes (American Diabetes Association, 2011). Men are slightly more likely to have diabetes than women, and non-Hispanic blacks have higher prevalence rates compared with non-Hispanic whites, Asian Americans, and Hispanics. Within this group, nearly 7 million adults over the age of 55 have also been diagnosed with CHD, and nearly 2 million of these people suffer from a CHD event annually[23]. This suggests that total expenditures on direct medical costs associated with diabetes-attributed CHD events were $26.4 billion in 2012.

23 Based on the Frost & Sullivan analysis of the National Health and Nutrition Examination Survey (National Health and Nutrition Examination Survey, 2010)

The total cumulative direct health care costs related to diabetes-attributed CHD events is expected to be over $260 billion from 2013 to 2020 among all diabetics over the age of 55 diagnosed with CHD.

Figure 5.1—Total Expenditure Forecast of Diabetes-attributed CHD Events among All Diabetic Adults over the Age of 55 with CHD, 2013–2020



	2013	2014	2015	2016	2017	2018	2019	2020
Event Spending ($ B)	28.80	29.80	30.86	31.99	33.18	34.43	35.78	37.21
Events (M People)	2.1	2.1	2.1	2.2	2.2	2.2	2.3	2.3

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

Projecting these per-person expenditures forward at an average compound annual growth rate of 5% from 2013 to 2020 and assuming an average compound annual target population growth rate of 1.7% during the same period, it is expected that an average of 2.2 million diabetic adults over the age of 55 and 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 cost of $16,690 per person (Agency for Healthcare Research and Quality—MEPS). 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 more than $262.05 billion over the forecast period; additionally, the annual average direct health care costs related to CHD events among this target population will be nearly $33 billion per year.

Multiple studies suggest that the use of chromium picolinate dietary supplements has a substantiated preventive effect on diabetes-attributed CHD events, which will be explored in detail in this chapter.

Figure 5.2—Diabetes-attributed CHD events Cost Summary for All Diabetic Adults over the Age of 55 Diagnosed with CHD, 2012–2020

Metric	Measure
Population of adults over the age of 55 diagnosed with type 2 diabetes, 2012	17,021,840
Population of type 2 diabetics with CHD, 2012 (People high-risk of experiencing an event)[24]	6,973,705
Population of type 2 diabetics with CHD who experienced a diabetes-attributed CHD-related inpatient procedure and/or visited the emergency room, 2012	1,980,116
Event rate—percent of the high-risk population that will experience a CHD event, (ER)	12%
Diabetes-attributed CHD hospital utilization event spending (inpatient procedures and emergency room visits), 2012[25]	$26.37 B
Expected average annual diabetes-attributed CHD hospital utilization event spending (inpatient procedures and emergency room visits), 2013–2020	$32.76 B
Cumulative diabetes-attributed CHD hospital utilization event spending (inpatient procedures and emergency room visits), 2013–2020	$262.06 B
Average claimed expenditures per person per year, 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

The biochemical mechanism of chromium on diabetes may be related to chromium's interaction with insulin receptors on cell surfaces.

Chromium picolinate

Literature Review

The form of chromium found in food and supplements is trivalent chromium, which is an essential trace mineral in human nutrition (Memorial Sloan-Kettering Cancer Center, 2013). Chromium is essential to insulin action in the metabolism of glucose (Memorial Sloan-Kettering Cancer Center, 2013). The biochemical mechanism of chromium is under study but may be related to chromium's interaction with insulin receptors on cell surfaces (Memorial Sloan-Kettering Cancer Center, 2013). Among the many dietary sources of chromium are meat, eggs, whole grains, broccoli, and beans (Memorial Sloan-Kettering Cancer Center, 2013). Of the forms of chromium for dietary supplementation, the picolinate form is more common because of its higher bioavailability.

The IOM has established adequate intake levels for chromium of 20 mcg per day for women over 50 and 30 mcg per day for men over 50 (Office of Dietary Supplements, 2005). There is insufficient data to establish a LOAEL, NOAEL or UL for trivalent chromium because "[n]o adverse effects have been convincingly associated with excess intake of chromium from food or supplements, but this does not mean that there is no potential for adverse effects resulting from high intakes" (Institute of Medicine, 2001).

24 Includes all diabetes-attributed events such as angina pectoris, heart attack, or any other heart condition or disease events.

25 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 outpatient or office-based provider visits, hospital inpatient stays, and emergency room visits.

Because of its role in insulin action, many studies have been undertaken to investigate possible benefits of chromium supplementation on subjects with diabetes, particularly type 2 diabetes. To quantify the possible effects of chromium supplementation on the occurrence of diabetes-related CHD events, a systematic search was conducted that focused on published studies of chromium supplementation on glycated hemoglobin (HbA1c) levels in diabetes. HbA1c is a common measure of glycemic control in diabetes, and it is also correlated with the rate of CHD. Ray et al., (2009) estimated from a systematic review of five RCTs involving more than 33,000 subjects undergoing intensive glucose-lowering regimens that a 0.9% reduction in HbA1c concentration correlates with a 15% reduction in CHD events (Ray, et al., 2009). This correlation was assumed to hold for the purposes of this study in order to model health care savings because of improved glycemic control from chromium supplementation. In addition, because of this substantiated direct link between improved glycemic control and a reduction in the risk of a CHD event among those who have type 2 diabetes, the focus of the cost model explored the direct effect of intensive chromium picolinate supplementation on direct medical costs related to only CHD events.

A PubMed literature search was conducted to identify a set of studies that represented the purported link between chromium supplementation and CHD risk. Only studies that tested for a causal relationship between supplement intake and the level of HbA1c were identified. Only studies similar in protocol in an attempt to control for observable variance were included in the analysis. Studies were not selected on the basis of the magnitude, direction or statistical significance of the reported findings. A total of 30 studies matching keyword combinations such as “chromium picolinate”; “diabetes” and/or “coronary heart disease”; and “risk reduction” were identified in the rigorous search. Of the reported study methods, randomized controlled trials (including crossover studies) were preferred because they are designed to directly test for a cause-and-effect relationship between chromium picolinate supplementation and the desired HbA1c reduction outcome. The search was conducted between February 1 and March 31, 2013.

Four RCT studies were identified as being representative of the indirect relationship between dietary supplement intake and the risk of a CHD-attributed disease event through the HbA1c biomarker. All four studies included subjects who had been diagnosed with type 2 diabetes. The studies compared a treatment group that received a daily chromium picolinate supplement regimen versus a placebo group. In the single crossover study, subjects took either chromium or placebo for a period, followed by a washout period, and then switched to the opposite product. Chromium supplementation was given for between three weeks and six months, depending on the study.

Figure 5.3—Chromium Picolinate Literature Review: Description of the Qualified Studies—Summary of Findings

Author	Year	Study details	Total sample (N)	Net percentage point change in HbA1c among treatment group versus control due to intensive chromium picolinate supplementation (%)
Albarracin	2008	RCT - Type 2 diabetic subjects; change in HbA1c with Cr vs. placebo is significantly different. Dose size was 600 mcg.	348	0.20
Anderson	1997	RCT - Type 2 diabetics. Dose size was 1000 mcg.	120	2.10
Ghosh	2002	Crossover Design - Type 2 diabetics in India. Dose size was 400 mcg.	50	0.70
Rabinovitz	2011	RCT - Elderly type 2 diabetics in Israel. Dose size was 400 mcg.	78	0.60
Sample Size Weighted Average				0.83
Reduction in the Relative Risk of a CHD Event for a .9 Percentage Point Decrease in HbA1c Levels (%)				15.0%[26]
Reduction in the Relative Risk of a CHD Event Given Intensive Chromium Picolinate Supplementation (%)				10.2%

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

Albarracin (2008) studied 447 U.S. overweight type 2 diabetics (Albarracin, Fuqua, Evans, & Goldfine, 2008). The treatment patients received a chromium supplement (600 mcg/day as picolinate) along with biotin, while the placebo group received neither. Biotin, a B vitamin, was included because it may also play a role in carbohydrate metabolism. After 90 days of supplementation, the chromium group showed a decrease in HbA1c of 0.54%, which was significantly different from the decrease of 0.34% in the control group. Anderson (1997) studied 180 type 2 diabetics in the U.S. The treatment group received 1000 mcg per day of chromium picolinate (Anderson, et al., 1997). After four months, the HbA1c levels in the treatment group averaged 6.6%, compared to 8.5% in the placebo group. Ghosh et al., (2002) studied 50 type 2 diabetics in India in a randomized, crossover trial lasting 12 weeks per treatment (Ghosh, et al., 2002). Chromium was supplemented as picolinate at 400 mcg/day. After chromium supplementation, the average HbA1c levels remained unchanged; however, they increased significantly in the placebo group by 0.7%, revealing a net benefit of chromium.

Finally, Rabinovitz et al., studied 78 diabetics of average age 78 years in Israel. Half received 400 mcg of chromium picolinate daily as well as standard treatment for diabetes, while the control half received standard treatment but no chromium supplement. After three weeks the HbA1c levels of the treatment group declined by 0.6%.

26 Ray, et al., 2009

An average of 81,243 CHD events could potentially be avoided annually from 2013-2020 if all diabetics over the age of 55 diagnosed with CHD were to use chromium picolinate dietary supplements at protective levels of intake. This amounts to 649,944 avoided events over the entire period.

Empirical Results

Given the literature review of the key qualified studies, it is estimated that the calculated relative risk reduction of a diabetes-attributed CHD event among patients over the age of 55 who have been diagnosed with CHD and given chromium picolinate dietary supplements at preventive daily intake levels was 10.2%. This estimate was deduced after controlling for variance due to sample size, research methodologies and study protocols, and patient population differences within each study and among all studies.

Figure 5.4—Chromium Picolinate Literature Review: Summary Results—CEBM Approach

Metric	Measure
Weighted relative risk reduction (weighted for inter-study variance) (RRR)	10.2%
Event rate (ER)	12%
Number of people needed to treat to avoid one diabetic-attributed CHD event (NNT), people	95
Average number of events CHD avoided annually if everybody in the target population* used chromium picolinate, 2013–2020	81,243
Cumulative number of events CHD avoided if everybody in the target population* used chromium picolinate, 2013– 2020	649,944

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

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Using the CEBM approach (Center for Evidence Based Medicine, 2012) to calculate NNT, 95 people would have to be treated with an intensive regimen of chromium picolinate supplements (over 400 mcg per day) to avoid one diabetes-attributed CHD event. This calculation takes into account the 12% odds of a diagnosed diabetic person over the age of 55 experiencing a CHD event during a year. Given the NNT of 95 people, which is achievable if every high-risk person in the target population were to take at least 400 mcg of chromium picolinate daily, avoided hospital utilization expenditures related to diabetes-attributed CHD events would average $1.2 billion per year—a cumulative savings of $9.75 billion from 2013 to 2020, assuming an annual average cost per person experiencing a CHD-related event of $16,690. This equates to an annual average of 81,243 avoided events from 2013 to 2020—649,944 cumulative avoided events.

For the purposes of this study, a daily dosage was assumed to be equal to or more than 400 mcg per day. Based on the review of qualified scientific literature, researchers treated their respective groups with intensive regimens of chromium picolinate on the order of 400 to 1000 mcg per day. Based on a review of chromium dietary supplement products on the retail market, the majority of such products contain at least 400 mcg of chromium picolinate per serving. Thus, it was determined that the cost of a daily dose of an intensive regimen of chromium picolinate ranges from $0.03 to $0.18. The median daily cost to the consumer is $0.09. Using this figure, the expected annual supplementation cost would average $248.7 million per year for the total target population—nearly $2.0 billion from 2013 to 2020.

Thus, the net savings, after accounting for the cost of chromium picolinate dietary supplementation, would average $970.0 million per year—nearly $7.80 billion cumulatively from 2013 to 2020. See Figures 8.17 to 8.20 in the appendix for a detailed reporting of the empirical results.

An average of $1.22 billion per year and a cumulative savings of $9.75 billion from 2013 to 2020 in avoidable hospital utilization costs is potentially realizable if all diabetics over the age of 55 diagnosed with CHD were to use chromium picolinate dietary supplements at preventive daily intake levels.

Figure 5.5—Chromium Picolinate Cost Analysis: Summary Results—Cost of Dietary Supplementation of the Target Population*, 2013–2020

Metric	Measure
Median daily cost of chromium picolinate supplementation at protective intake levels, 2013	$0.09
Expected annual median cost of chromium picolinate supplementation at protective intake levels, 2013	$34.67
Average annual cost of chromium picolinate dietary supplementation of the target population*, 2013–2020	$248.7 M
Cumulative cost of chromium picolinate dietary supplementation of the target population*, 2013–2020	$1.99 B

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

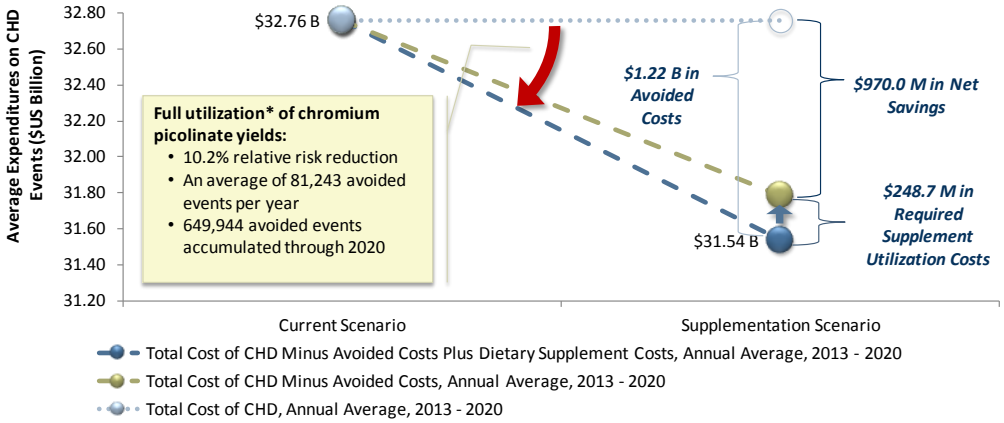
Figure 5.6—Chromium Picolinate Cost Analysis: Summary Results—Avoided Hospital Utilization Expenditures* due to Dietary Supplement Intervention, 2013–2020

Metric	Measure
Average annual avoided hospital utilization expenditures related to CHD if incidence is reduced through the use of chromium picolinate supplements, 2013–2020	$1.22 B
Cumulative avoided hospital utilization expenditures related to CHD if incidence is reduced through the use of chromium picolinate supplements, 2013–2020	$9.75 B
Average annual hospital utilization expenditures for CHD-related events among the target population* if incidence is reduced through the use of chromium picolinate supplements, 2013–2020	$31.54 B
Cumulative hospital utilization expenditures for CHD-related events among the target population* if incidence is reduced through the use of chromium picolinate supplements, 2013–2020	$252.30 B

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

Over $7.75 billion in cumulative net CHD-attributed cost savings from 2013 to 2020 is potentially realizable if the entire target population were to use chromium picolinate dietary supplements at protective intake levels.

Figure 5.7—Chromium Picolinate Cost Analysis: Net Health Care Cost Savings* Summary Results, 2013–2020



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

Figure 5.8—Chromium Picolinate 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 chromium picolinate supplement intervention, 2013–2020	$970.0 M
Cumulative net potential direct savings from avoided CHD hospital utilization events due to chromium picolinate dietary supplement intervention, 2013–2020	$7.76 B
Net benefit cost ratio, $ per one dollar spent on dietary supplement	$3.90

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

Conclusion

The chromium picolinate cost-benefit analysis assumes that in the supplementation scenario all diabetic adults over the age of 55 with CHD use chromium picolinate at protective 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 that are realizable. However, because it is likely that less than 1% of diabetic adults over the age of 55 are regular users of chromium picolinate dietary supplements because of the low awareness of its health benefits, nearly all of the $970.0 million in potential net savings has yet to be realized. Thus, it is expected that there are significant cost savings yet be realized through the increased usage of chromium picolinate dietary supplements among the high-risk target population.

It is expected that less than 1% of adults over the age of 55 are already regular users of chromium picolinate dietary supplements, suggesting that nearly all of the potential net cost health care savings have yet to be realized.

Overall, the scientific evidence suggests that the use of chromium picolinate helps to lower HbA1c levels; thus, the potential health care cost savings derived from its use is expected to be significant. Specifically, if one were to only look at the potential avoided costs of diabetes-attributed CHD events among diabetics over the age of 55 with diagnosed CHD, the total cost savings derived from avoided CHD events would average $970.0 million per year—nearly $7.80 billion cumulatively over the forecast period—after accounting for the cost of chromium picolinate dietary supplementation. This equates to a significant $3.90 that can be saved per $1 spent on chromium picolinate, in terms of the ratio of avoided CHD-related costs because of supplementation per $1 spent on the supplements. This is primarily because chromium picolinate is shown to be essential to insulin action in the metabolism of glucose, and its overall cost to consumers is low.

Based on the findings of this study, chromium picolinate is suggested to be a key component maintenance regimen for type 2 diabetics at high risk of suffering a CHD event; however, more scientific research should be undertaken to test this hypothesis to avoid the use of indirect means to calculate treatment numbers needed to avoid one CHD event. In addition, the inability to effectively metabolize glucose leads to other potential problems, including vision disabilities, feet and renal problems, and general mobility issues, all of which add to the total cost of diabetes. The true potential cost savings could be significantly greater than what is presented in this case study, which confirms the need for more scientific research that tests the direct link between lower HbA1c levels and lower diabetes-attributed CHD events to further substantiate the importance of chromium picolinate's role in helping to control growth in societal health care costs.

AGE-RELATED EYE DISEASE AND THE COST EFFECTIVENESS OF USING LUTEIN AND ZEAXANTHIN

Prevalence and Social Consequences

Age-related macular degeneration (AMD) and cataracts are serious ophthalmic conditions that threaten the vision of a large percentage of the United States' elderly population and pose a significant financial burden. AMD and cataracts together are often referred to as Age-Related Eye Disease (ARED).

AMD affects the central part of the retina known as the macula (National Eye Institute, 2009). The macula is approximately 2 centimeters wide and is in the center of the retina. The two forms of AMD are wet and dry. Wet, or exudative, AMD occurs when irregular blood vessels begin to form underneath the macula (National Eye Institute, 2009). The blood vessels generally leak blood and fluid, raising the macula and distorting central, straightforward vision. Wet AMD is the most aggressive form of AMD, and visual impairment can occur in a short time. Wet AMD recently has attracted much scientific attention because of advances in therapeutic technology (National Eye Institute, 2009).

Dry AMD occurs when photoreceptors in the eye deteriorate and form fatty deposits (drusen) in the layer of cells underneath the retina (National Eye Institute, 2009). Dry AMD progresses slowly and generally affects the central vision over the course of many years. Many people who have AMD in only one eye may not experience any changes in visual acuity; however, if AMD affects both eyes, there will be a distortion in central vision, and more advanced cases will experience blurred gray spots in the straight-ahead vision field. AMD causes a blurred spot in central vision because it primarily affects the macula (National Eye Institute, 2009).

Dry AMD, which accounts for about 90% of diagnosed cases, is considered the early, and less severe, stage in the overall progression of the disease. (National Eye Institute, 2009) The more severe wet AMD accounts for the remaining 10% diagnosed cases and is responsible for the majority of AMD vision loss cases. Thus, those with the wet form have a greater prevention and therapeutic need. Therapies in development to halt the disease in its early stages may prevent the progression and catastrophic vision losses associated with the wet form.

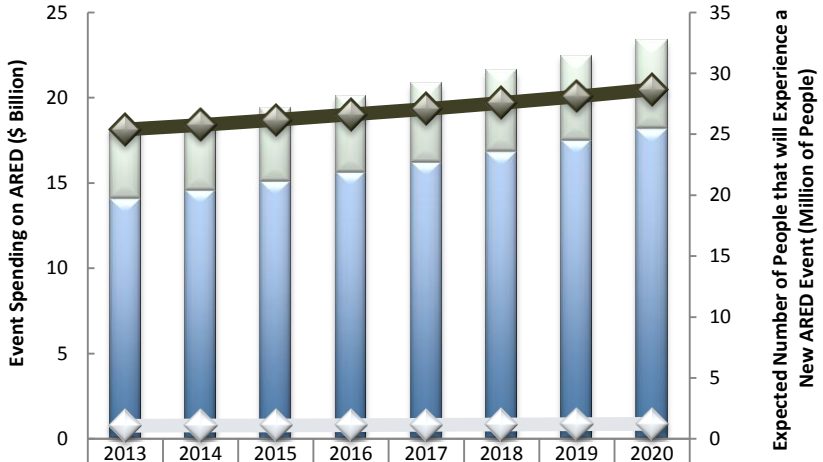
The total cumulative health care costs related to AMD and cataract events among all U.S. adults over the age of 55 diagnosed with ARED is expected to be over $164 billion from 2013 to 2020.

Cataracts (clouding in the lens) are the result of the clumping together of proteins (National Eye Institute, 2009). As the cataract grows, visual acuity is decreased. Risk factors for developing cataracts are overexposure to ultraviolet light and radiation, as well as diabetes and hypertension.

In 2012, the total direct medical costs associated with AMD and cataracts, plus the related expected costs of post-procedure nursing care/assisted living services, was estimated at almost $17.00 billion among all U.S. adults over the age of 55 (Agency for Healthcare Research and Quality—MEPS, Assisted Living Facilities.org, 2012, and Frost & Sullivan analysis). In the same year, an estimated 2.1 million people developed wet AMD, which can result in vision loss in as few as six months (Agency for Healthcare Research and Quality—MEPS). Furthermore, cataract prevalence in 2012 was 25.0 million Americans in the United States (Agency for Healthcare Research and Quality—MEPS). More than 3.7 million Americans over the age of 55 suffered from a cataract event and pursued surgery or other direct hospitalization services to treat the condition in 2012 (Agency for Healthcare Research and Quality—MEPS).

Cataracts and AMD can also limit independence and the ability to perform daily activities, which often results in additional indirect costs and significant emotional distress that affects quality of life. Specifically, an estimated 5% of all people over the age of 55 who suffer from a age-related eye disease (27.2 million people) will require post-procedure nursing care/assisted living services that averages about $59,000 per year (Assisted Living Facilities.org, 2012).

Figure 6.1—Total Expenditure Forecast for Age-related Eye Disease-related Events among All U.S. Adults over the Age of 55, 2013–2020



	2013	2014	2015	2016	2017	2018	2019	2020
AMD Event Spending ($ B)	4.00	4.14	4.29	4.44	4.61	4.78	4.97	5.17
Cataract Event Spending ($ B)	14.07	14.56	15.08	15.63	16.21	16.82	17.48	18.18
AMD Events (M People)	1.1	1.1	1.1	1.1	1.1	1.2	1.2	1.2
Cataract Events (M People)	25.4	25.8	26.2	26.6	27.1	27.6	28.1	28.7

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

Through 2020, an average of 4.8 million people over the age of 55 will experience a costly AMD or cataract event. This implies that the total cumulative health care costs related to ARED events among the target population will be more than $164.40 billion—an average annual cost of nearly $20.60 billion.

Multiple studies suggest that the use of lutein and zeaxanthin dietary supplements have a preventive effect on age-related eye disease. This will be explored in detail in this chapter.

The carotenoid pigments lutein and zeaxanthin are expected to play roles in protecting the eye from oxidative damage caused by light interacting with other pigments in the retina.

Figure 6.2—Age-related Eye Disease Events Cost Summary for All U.S. Adults over the Age of 55, 2012 – 2020

Metric	Measure
Population diagnosed with age-related eye disease, 2012[27]	27.2 M
Expected number of adults over the age of 55 who will experience an age-related macular degeneration event, 2012[28]	1.1 M
Expected number of adults over the age of 55 who will experience an age-related cataract event*, 2012	3.7 M
Event rate—percent of the high risk population that will experience an ARED event, 2012 (ER)	33%
Total expenditures on age-related eye disease treatment procedures and post-procedure nursing care/assisted living services , 2012	$16.97 B
Average annual hospital utilization expenditures ARED events among all U.S. adults over the age of 55 with ARED forecast , 2013–2020	$20.55 B
Mean expenditures per person per year suffering from ARED, 2012[29]	$3,535
Expected mean expenditures per person per year suffering from ARED, 2013–2020	$4,431

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

27 The total population of age-related eye disease sufferers includes all people diagnosed with age-related macular degeneration and/or cataracts.

28 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 outpatient or office-based provider visits, hospital inpatient stays, and emergency room visits.

29 Mean expenditures per person per year suffering from age-related eye disease is defined as the sum of both expected direct medical costs per person experiencing an event per year (an average of $243.57 per year) plus the expected costs of post-procedure nursing care/assisted living services (an average of $59,262 per year for 5% of event sufferers, or an average of $3,535.35 over the whole population of event sufferers).

Lutein and Zeaxanthin

Literature Review

Lutein and zeaxanthin are xanthophylls, a type of carotenoid pigment (Memorial Sloan-Kettering Cancer Center, 2013). They are found in high concentrations in the macula. Lutein and zeaxanthin are believed to play roles in protecting the eye from oxidative damage caused by light interacting with other pigments in the retina (Memorial Sloan-Kettering Cancer Center, 2013). Lutein and zeaxanthin are not synthesized by the body; major sources from dietary consumption include dark leafy vegetables such as spinach and kale, eggs, corn, and peppers (Memorial Sloan-Kettering Cancer Center, 2013).

In dry AMD, the concentration of pigments in the central part of the macula declines. Some studies have demonstrated that increasing dietary supplementation with lutein and/or zeaxanthin in AMD patients leads to an increase in macular pigment and improved visual acuity. Other studies, described below, link high dietary intake of lutein and zeaxanthin with decreased risk of AMD.

Lutein and zeaxanthin may also play a role in inhibiting the formation of cataracts. The protective effects of these pigments may prevent eye lens damage from ultraviolet light, which is believed to be a cause of cataracts. A few studies described below correlate high dietary intake of lutein and zeaxanthin with reduced incidence of cataracts.

In the United States, there is no government-recognized recommended daily intake level for lutein and zeaxanthin, but the American Optometric Association (AOA) suggests that 10 mg per day of lutein and 2 mg per day of zeaxanthin benefits eye health based on results of recent scientific studies. This is assumed to be sufficient to derive the expected benefits explored in this study (American Optometric Association, 2013). Carotenoids, including lutein and zeaxanthin, are discussed in the IOM volume on DRIs for antioxidant nutrients. However, no DRIs or UL have been established for carotenoids as a group or for any specific carotenoids (Institute of Medicine, 2000).

To deduce the expected efficacy of a treatment with lutein and zeaxanthin on the occurrence of an ARED event (AMD or cataract), a systematic search was conducted that focused on published studies that tested for and quantified the effect of their supplementation on ARED incidence requiring medical treatment and post-procedural care. The objective was to identify the best set of studies that tested for a direct causal relationship between intake of the dietary supplement and the relative risk of a disease event, and included studies similar in protocol in an attempt to control for observable variance. Studies were not selected on the basis of the magnitude, direction or statistical significance of the reported findings. A rigorous PubMed search identified more than 25 studies based on keyword combinations such as “lutein” and/or “zeaxanthin”; “macular degeneration” and/or “cataract”; and “risk reduction.” The search was conducted between February 1 and May 31, 2013.

Eleven studies including RCTs, prospective cohort studies, and cohort epidemiological studies were identified as being representative of the literature. Of the studies on AMD, one RCT and three case-controlled or cohort epidemiological studies were identified and selected for analysis. For cataracts, one RCT and six case-controlled or cohort epidemiological studies were selected. The studies are described below.

Figure 6.3—Lutein and Zeaxanthin Literature Review: Description of the Qualified Studies

Author	Year	Event definition
Chew	2013	Progression to advanced AMD
SanGiovanni	2007	Neovascular AMD, geographic atrophy, or large or intermediate Drusen
Seddon	2010	Overall AMD (combined geographic atrophy and neovascular AMD)
Seddon	1994	AMD
Tan	2008	Neovascular AMD and geographic atrophy
Brown	1999	Cataract extraction in men
Chasan-Taber	1999	Cataract extraction in women
Chew (AREDS2)	2013	Progression to cataract surgery
Christen	2008	Incidence of cataracts in women
Jacques	2001	Prevalence of nuclear opacities in non-diabetic women
Vu	2006	Prevalence of nuclear cataract

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

Seddon et al., (1994) conducted a case-controlled study that matched 356 people in the U.S. with advanced AMD with a control group of 520 persons with other eye diseases (Seddon, et al., 1994). The relative risk of AMD was estimated according to various indicators, including dietary components. In comparing the highest and lowest quintiles of lutein and zeaxanthin intake, the authors found a statistically significant reduction in the risk of AMD (odds ratio 0.57, 95% CI 0.35 to 0.92). SanGiovanni et al., (2007) conducted another case-controlled study of 4,519 subjects in the U.S., most of whom had some degree of AMD (SanGiovanni, et al., 2007). Data on dietary intake were analyzed and tested versus AMD incidence. A statistically significant reduction in neovascular AMD incidence (odds ratio 0.65; 95% CI 0.45 to 0.93) was identified in comparing the highest and lowest quintiles of lutein and zeaxanthin intake. Tan et al., (2008) conducted a population-controlled cohort study of diet and AMD incidence in 3,654 participants in Australia (Tan, Wang, Flood, Rochtchina, Smith, & Mitchell, 2008). Participants in the highest tertile of dietary lutein and zeaxanthin intake had a relative risk for incident AMD of 0.35 (95% CI 0.13 to 0.92). Seddon et al., (2010) compared 545 subjects with AMD to 275 subjects without AMD in a case-controlled study (Seddon, Reynolds, & Rosner, 2010). In comparing the highest and lowest tertile of lutein intake, the odds ratio for overall risk of AMD was 0.6 (95% CI 0.4 to 1.0).

Another study included in this analysis is Age-Related Eye Disease Study II (AREDS2), a randomized, controlled trial testing dietary supplements in 4,203 subjects at risk for progression to advanced AMD (Chew et al., 2013). All participants took a daily formulation of vitamins C and E, beta carotene, zinc, and copper, which in an earlier AREDS randomized controlled study (Age-Related Eye Disease Study Research Group, 2001) was shown to reduce the risk of developing advanced AMD. In AREDS2, a group of participants additionally took a daily supplement of lutein (10 mg) and zeaxanthin (2 mg). Eye examinations were conducted over a median of 5 years to assess progression to advanced AMD. The primary analysis compared subjects supplemented with the AREDS formulation and lutein plus zeaxanthin to those supplemented with AREDS formulation only. The hazard ratio for progression to advanced AMD was 0.90 for the lutein plus zeaxanthin group (98.7% CI 0.76 to 1.07). This is the value Frost & Sullivan used in the analysis of risk reduction, combined with the above-mentioned observational studies (Figure 6.4). However subgroup and secondary analyses in AREDS2 suggest that lutein plus zeaxanthin supplementation may result in even lower hazard ratios for AMD. For example, the hazard ratio was 0.74 (98.7% CI 0.59 to 0.94) for progression to advanced AMD in participants with the lowest quintile of dietary lutein and zeaxanthin intake. Also, for a subgroup that received lutein plus zeaxanthin and a variant of the AREDS formulation that lacked beta carotene, a hazard ratio of 0.82 (95% CI 0.69 to 0.96) for progression to advanced AMD was found. Only the primary result was used for the present analysis, rather than subgroup and secondary results of Chew et al., to maintain consistency with analyses of other supplements in the present study.

Studies linking dietary consumption of lutein and/or zeaxanthin to primary prevention of cataracts were also identified. One randomized controlled trial and six prospective cohort or epidemiological studies were identified and selected for analysis, as described below.

In a prospective cohort study, Brown et al., (1999) followed the dietary intake of 36,644 male health care professionals in the United States for 8 years and quantified the incidence of cataract extractions (Brown, et al., 1999). When comparing the highest and lowest quintiles of lutein and zeaxanthin intake, the risk of cataract extraction was 19% lower (95% CI 0.65 to 1.01) in the high-intake group. Chasan-Taber et al., (1999) prospectively examined the association between lutein and zeaxanthin intake and the incidence of cataract extractions among 77,466 U.S. women over a period of 12 years (Chasan-Taber, et al., 1999). Comparing subjects in the highest quintile with those in the lowest quintile of lutein and zeaxanthin intake, the relative risk of cataract extraction was 0.88 (95% CI 0.75 to 1.03). Jacques et al., (2001) conducted a prospective cohort study of 478 non-diabetic U.S. women over 13 to 15 years (Jacques, et al., 2001). Nutrient intake was evaluated and tested against the incidence of cataracts, measured as nuclear lens opacities. The prevalence of cataracts was significantly lower in the highest quintile of lutein/zeaxanthin intake than in the lowest quintile, with an odds ratio of 0.52 (95% CI 0.29 to 0.91). Vu et al., (2006) studied nuclear cataract prevalence in 1,955 people in Australia (Vu, Robman, Hodge, McCarty, & Taylor, 2006). For those in the top quintile of lutein and zeaxanthin intake the odds ratio for nuclear cataracts was 0.58 (95% CI 0.37 to 0.92). Christen et al., (2008) prospectively studied more than 35,000 U.S. women over 10 years, evaluating nutrient intake and self-reported cataract incidence (Christen, Liu, Glynn, Gaziano, & Buring, 2008). The relative risk of cataracts in the highest quintile of lutein/zeaxanthin intake was 0.82 (95% CI 0.71 to 0.95) compared with the lowest quintile.

The AREDS2 clinical trial also is included in this analysis in the context of cataracts. Chew et al., followed the 4,203 AREDS2 subjects for a median 4.7 years to document cataract surgeries (Chew et al, 2013). That analysis compared subjects supplemented with lutein plus zeaxanthin to those who did not receive these ingredients. The hazard ratio for cataract surgery was 0.96 for the lutein plus zeaxanthin group (98.7% CI 0.84 to 1.10). Frost & Sullivan used this study value in its analysis of risk reduction, combining results from the above-mentioned observational studies of cataracts (Figure 6.5).

Figure 6.4—Lutein and Zeaxanthin Literature Review: Description of the Qualified Studies—Summary of Findings, Age-related Macular Degeneration

Author	Total sample (N)	AMD relative risk (RR) for lutein and zeaxanthin, hazard ratio or top versus bottom quantile	Study weights based on sample size variance
Chew (AREDS2)	4,203	0.90**	43.3%
SanGiovanni	1,772	0.65*	18.3%
Seddon	820	0.60*	8.4%
Seddon	876	0.57*	9.0%
Tan	2,035	0.77***	21.0%
Estimated relative risk		77.0%	

* Odds ratio, top versus bottom quintile
** Hazard ratio compared to no treatment
*** Relative risk, top versus bottom tertile

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

An average of 14,406 AMD events per year and an average of 957,318 cataract events per year could potentially be avoided if all U.S. adults over the age of 55 diagnosed with ARED were to use lutein and zeaxanthin dietary supplements at protective levels during the forecast period.

Figure 6.5—Lutein and Zeaxanthin Literature Review: Description of the Qualified Studies—Summary of Findings, Age-related Cataracts

Author	Total sample (N)	Cataracts relative risk (RR) for lutein and zeaxanthin, hazard ratio or top versus bottom quintile	Study weights based on sample size variance
Christen	35,551	0.82	22.7%
Jacques	478	0.52*	0.3%
Brown	36,640	0.81	23.4%
Chasan-Taber	77,466	0.88	49.6%
Vu	1,955	0.58*	1.3%
Chew (AREDS2)	4,203	0.96**	2.7%
Estimated relative risk		0.85	

* Odds ratio
** Hazard ratio compared to no treatment

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

Empirical Results

Based on the results of the literature review, it was determined that 95 people would need to be treated with lutein and zeaxanthin to avoid one age-related macular degeneration event, and 23 people would need to be treated with lutein and zeaxanthin to avoid one cataract event. Both of these NNT estimates were calculated using the CEBM approach.

Given the NNT for AMD of 159 people, if every person over the age of 55 with ARED were to take lutein and zeaxanthin supplements at the preventive daily intake levels, avoided expenditures related to AMD would average $57.4 million per year—a cumulative savings of $458.8 million from 2013 to 2020. This savings is based on an average expenditure per person experiencing an ARED event of $4,431, which includes direct medical costs and post-procedure assisted living costs. This equates to an annual average of 14,406 avoided AMD events from 2013 to 2020—115,248 cumulative AMD avoided events.

Regarding the NNT for cataracts of 28 people, the effect on avoided direct medical costs and post-procedure assisted living costs related to cataracts given the daily use of lutein and zeaxanthin supplements at preventive levels would average $3.8 billion per year, for a cumulative savings of $30.5 billion from 2013 to 2020. This is associated with an annual average of 957,318 avoided cataract events from 2013 to 2020—7,658,543 cumulative avoided events. See Figures 8.21 to 8.25 in the appendix for a detailed reporting of the empirical results.

Figure 6.6—Lutein and Zeaxanthin Literature Review: Overall Results—CEBM Approach

Metric	Measure
Expected event rate of AMD among the target population* (ER_{ADM})	2.8%
Expected event rate of cataracts among the target population* ($ER_{CATARACTS}$)	33.0%
Weighted AMD event relative risk (weighted for sample size variance) (RR_{ADM})	77.0%
Weighted Cataracts event relative risk (weighted for sample size variance) ($RR_{CATARACTS}$)	84.7%
Estimated number of people needed to be treated to avoid one age-related macular degeneration event (NNT_{AMD})	159
Estimated number of people needed to be treated to avoid one cataract event ($NNT_{CATARACTS}$)	28
Cumulative number of avoided age-related macular disease events, 2013–2020	115,248
Cumulative number of avoided cataract events, 2013–2020	7,658,543

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

Based on the review of best-selling products in leading brick-and-mortar, online, and mail-order retail establishments, the price of a daily dose of lutein and zeaxanthin, ranges from as low as $0.11 to as high as $0.57 for 1 daily dose. The median price per daily dose is $0.29.

Thus, the annual expected cost of lutein and zeaxanthin dietary supplementation for all U.S. adults over the age of 55 with AMD or cataracts would be $106.50 per person—more than $2.9 billion per year for the total sub-population, and more than $23.2 billion cumulatively from 2013 to 2020.

Figure 6.7—Lutein and Zeaxanthin Cost Analysis: Summary Results—Cost of Dietary Supplementation of the Target Population, 2013–2020

Metric	Measure
Median per person cost of lutein and zeaxanthin supplementation at protective intake levels, 2013	$0.29
Expected per person annual median cost of lutein and zeaxanthin supplementation at protective intake levels, 2013	$106.50
Average annual cost of lutein and zeaxanthin dietary supplementation of the target population*, 2013–2020	$2.90 B
Cumulative cost of lutein and zeaxanthin dietary supplementation of the target population*, 2013–2020	$23.22 B

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

An average of $3.87 billion per year and a cumulative savings of $30.95 billion from 2013 to 2020 in avoidable health care utilization costs is potentially realizable if all U.S. adults over the age of 55 diagnosed with AMD or cataract were to use lutein and zeaxanthin dietary supplements at protective levels

Over $7 billion in cumulative net ARED-attributed health care cost savings from 2013 to 2020 is potentially realizable if the entire target population were to use lutein and zeaxanthin dietary supplements at protective intake levels.

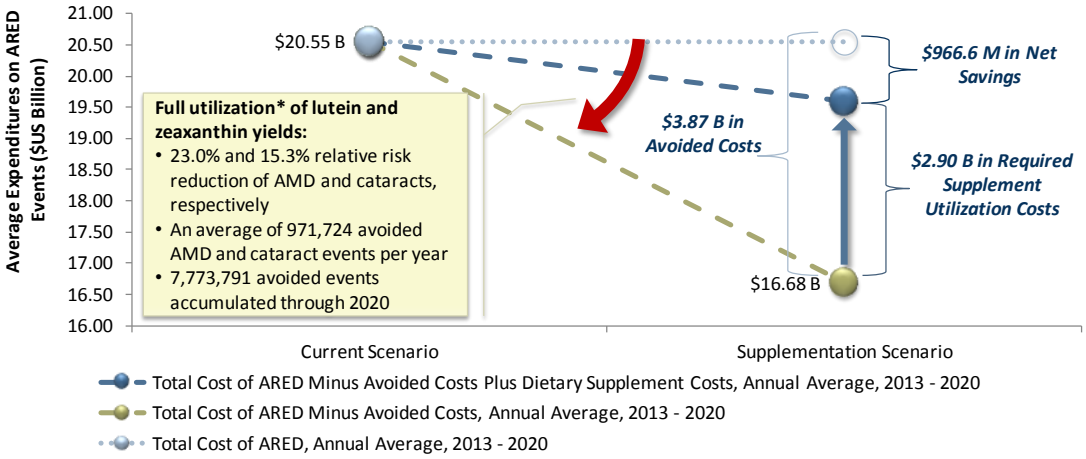
Figure 6.8—Lutein and Zeaxanthin Cost Analysis: Summary Results—Avoided Health Care Expenditures* due to Dietary Supplement Intervention, 2013–2020

Metric	Measure
Average annual avoided expenditures related to ARED as a result of lutein and zeaxanthin supplement intervention, 2013–2020	$3.87 B
Cumulative avoided expenditures related to ARED as a result of lutein and zeaxanthin supplement intervention, 2013–2020	$30.95 B
Average annual total expenditures on ARED-related events among the target population* if incidence of events is reduced through the use of lutein and zeaxanthin supplements, 2013–2020	$16.68 B
Cumulative total expenditures on ARED-related events among the target population* if incidence of events is reduced through the use of lutein and zeaxanthin supplements, 2013–2020	$133.48 B

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

Knowing that the total cost savings derived from avoided ARED events for the same population was, on average, $3.9 billion per year and nearly $31.0 billion cumulatively from 2013 to 2020, the net savings, after accounting for the cost of lutein and zeaxanthin dietary supplementation, would average $966.6 million per year and would be more than $7.7 billion cumulatively from 2013 to 2020.

Figure 6.9—Lutein and Zeaxanthin Cost Analysis: Net Health Care Cost Savings* Summary Results, 2013–2020



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

Figure 6.10—Lutein and Zeaxanthin Cost Analysis: Summary Results—Net Cost Savings* due to Avoided Health Care Expenditures through Dietary Supplement Intervention, 2013–2020

Metric	Measure
Average net potential direct savings per year from avoided ARED-related events among the target population* due to lutein and zeaxanthin supplement intervention, 2013–2020	$966.6 M
Cumulative net potential direct savings from avoided ARED-related events among the target population* due to lutein and zeaxanthin supplement intervention, 2013–2020	$7.73 B
Net benefit cost ratio, $ per one dollar spent on dietary supplement	$1.33

* Among all U.S. adults over the age of 55 with AMD or cataract.

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

It is expected that there are significant potential ARED-attributed cost savings yet to be realized valued at an annual average of nearly $1 billion per year if the use of lutein and zeaxanthin dietary supplements among current non-regular users in the high-risk target population were to increase their use to protective levels of intake.

The subsequent cost-benefit analysis assumes that in the supplementation scenario all people over the age of 55 with AMD or cataract use lutein and zeaxanthin 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 that are realizable. However, because a significant number of adults over the age of 55 are regular users of lutein and zeaxanthin dietary supplements, this segment of the target population already has a reduced risk of experiencing a costly ARED event and is already realizing the supplements' risk-reducing benefits.

According to the 2012 Council for Responsible Nutrition Consumer Survey on Dietary Supplements conducted by Ipsos Public Affairs, 4% of U.S. adults over the age of 55 are regular users of lutein dietary supplements (Ipsos Public Affairs, 2012)[30]. Because of the fact that the majority of lutein dietary supplement products in the market are often paired with zeaxanthin due to its near identical chemical composition and both nutrients are found to occur together in nature, it is also expected that zeaxanthin usage levels are similar in scale. This implies that 96% do not realize the potential benefits from regular use. Because avoided expenditures and net cost savings are a direct function of the total number of people in the target population using these 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.

30 It is not known what percentage of this target population segment also suffers from ARED events, but for the purposes of this analysis, Frost & Sullivan has made the assumption that approximately the same percentage (4%) of adults over the age of 55 with ARED are also regular users of lutein (and presumably zeaxanthin as well due to both nutrients close association). 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 lutein and zeaxanthin to provide a protective effect. More research is required to test these assumptions.

In addition to the direct health care costs attributed to AMD and cataracts, the intangible costs, such as the significant physical and emotional distress of ARED sufferers and their families are also additional burdens to consider in assessing the overall quality of life and consequently the total social cost of AMD and cataracts.

Knowing this, it is expected that $39.8 million of the $966.6 million net potential direct savings per year from avoided ARED events because of lutein and zeaxanthin dietary supplement intervention is already realized in the total expected ARED costs. This equates to an average of 932,855 avoidable events per year yet to be realized, and an average of $927.9 million per year in net savings yet to be realized—nearly $7.42 billion in cumulative net savings from 2013 to 2020. Thus, it is expected that there are significant cost savings yet be realized through the increased usage of lutein and zeaxanthin dietary supplements among the high-risk target population.

Figure 6.11—Lutein and Zeaxanthin Cost Analysis: Summary Results—Net Cost Savings* Yet to be Realized due to Avoided Health Care Expenditures through Dietary Supplement Intervention, 2013–2020

Metric	Measure
Percentage of the target population* who are regular users of lutein and zeaxanthin dietary supplements, 2012	4%
Average number of events avoided annually among the target population* yet to regularly use lutein and zeaxanthin, 2013–2020	932,855
Cumulative number of events avoided among the target population* yet to regularly use lutein and zeaxanthin, 2013–2020	7,462,840
Average net direct savings per year from avoided ARED-related events due to lutein and zeaxanthin dietary supplement intervention yet to be realized, 2013–2020	$927.9 M
Cumulative net direct savings per year from avoided ARED-related events due to lutein and zeaxanthin dietary supplement intervention yet to be realized, 2013–2020	$7.42 B

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

Conclusion

The estimated total expenditures on the direct medical costs associated with ARED events plus the related expected costs of nursing care/assisted living services because of reduced vision was almost $17.00 billion in 2012. Based on the findings of this report, the use of lutein and zeaxanthin dietary supplements could result in a savings of nearly $1.00 billion per year—more than $7.70 billion from 2013 to 2020. In other words, $1.33 in avoided costs can be saved per $1 spent on lutein and zeaxanthin supplements.

The key source of these potential costs is tied to expected post-ARED-event reduced vision, which results in an overall lower quality of life. Specifically, cataracts and AMD can limit a person's independence and ability to perform daily activities. In addition, intangible costs not captured in the analysis, such as significant physical and emotional distress of ARED sufferers, are additional burdens to consider in assessing overall quality of life. It is estimated that 5% of all people over the age of 55 who suffer from an ARED event will require costly post-ARED event nursing care/assisted living services that cost about $59,000 per year. These costs likely will fall on relatives or the government in the form of Medicare. Therefore, any means to help reduce these costs, including the adoption of key eye-health supplements that are shown to have a substantial health benefit, should be considered as a viable tool to reduce the burden of this disease and related financial costs.

OSTEOPOROSIS AND THE BENEFITS OF USING CALCIUM, VITAMIN D, AND MAGNESIUM

The total health care expenditure on managing and treating osteoporosis-attributed bone fractures among all U.S. women over the age of 55 with osteoporosis in the U.S. was over $14 billion per year in 2012.

Prevalence and Social Consequences

Osteoporosis is the most prevalent bone disease in the United States and is characterized by accelerated bone loss, which results in brittle and weak bones that are easily fractured. (PubMed Health, 2012) Normally, bones are continuously regenerated, with new bone replacing old bone. However, in older people this process is less efficient, and more bone is lost than is replaced. Patients with osteoporosis have an increased risk of fractures, particularly of the hip, spine, and wrist. (PubMed Health, 2012)

At the onset of osteoporosis, outward symptoms are not visible. However, it can gradually result in fractures caused by relatively normal activities, such as exercising or lifting heavy objects. These fractures can lead to pain, severe disability, or loss of mobility.

Post-menopausal women are at the highest risk of having osteoporosis, and it is especially prevalent among white and Asian women. After menopause, estrogen hormone levels fall. The hormone is vital in maintaining bone density by retaining calcium in the bones. After menopause, the rate of bone degeneration outpaces bone formation, resulting in the thinning of bones and development of osteoporosis.

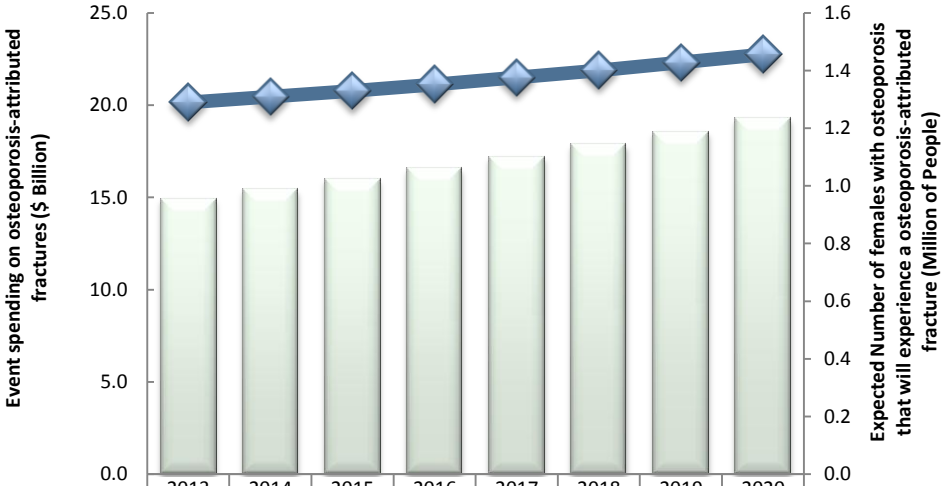
An estimated 8.2 million U.S. women over the age of 55 have developed osteoporosis. Among this target population, the number of fractures in the U.S. because of osteoporosis is as follows (Centers for Disease Control and Prevention, 2011; National Osteoporosis Foundation, 2013):

- More than 560,000 vertebral fractures
- More than 240,000 hip fractures
- More than 200,000 wrist fractures
- More than 240,000 other fractures

Thus, it is estimated that more than 1.2 million fracture events occurred in 2012 at an average treatment cost of $11,020 among women over the age of 55 with osteoporosis (Blume & Curtis, 2011, Agency for Healthcare Research and Quality, 2010, and Frost & Sullivan). This equates to more than $14.00 billion in annual direct health care costs just associated with treating the fracture; it excludes the added costs of lost productivity, mobility, and general quality of life.

The total cumulative direct health care costs related to osteoporosis-attributed bone fractures among all U.S. women over the age of 55 diagnosed with osteoporosis is expected to be nearly $136 billion from 2013 to 2020.

Figure 7.1—Total Expenditures Forecast for Osteoporosis-Attributed Fractures among Women over the Age of 55 diagnosed with Osteoporosis, 2013–2020



	2013	2014	2015	2016	2017	2018	2019	2020
Event Spending ($ B)	14.93	15.45	15.99	16.58	17.19	17.85	18.54	19.28
Events (M People)	1.29	1.31	1.33	1.35	1.38	1.40	1.43	1.46

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

Projecting these per-person expenditures forward at an average annual growth rate of 5% from 2013 to 2020 and assuming an average annual target population growth rate of 1.7% during the same period, it is expected that an average of 1.4 million women over the age of 55 and diagnosed with osteoporosis will experience a costly fracture and file a hospitalization claim. Hospitalization claims are defined as all inpatient hospitalizations and emergency room visits from 2013 to 2020, at an annual average per-person cost of $13,812 (Agency for Healthcare Research and Quality—MEPS). This implies that the total cumulative direct health care costs related to osteoporosis-attributed fractures among women over the age of 55 will be more than $135.81 billion over the forecast period—nearly $17.00 billion per year.

As osteoporosis becomes more prevalent in the U.S. due to the aging of America, new preventive options become more important as a means to control the financial burden of osteoporosis. Calcium, vitamin D, and magnesium are the key available dietary supplement options that have been shown to have a substantiated preventive effect on osteoporosis-attributed events. This will be explored in detail in this chapter.

Figure 7.2—Osteoporosis Cost Summary for All U.S. Women Over the Age of 55, 2012–2020

Metric	Measure
Population of women over the age of 55 with osteoporosis (people at high risk of experiencing an event), 2012[31]	8.2 M
Number of women over the age of 55 with osteoporosis that claimed an osteoporosis-attributed fracture, 2012	1.3 M
Event rate—percent of the high risk population that will experience an osteoporosis-attributed fracture, 2012 (ER)	15.1%
Total claimed expenditures on osteoporosis-related inpatient procedures and emergency room visits among all U.S. women over the age of 55 with osteoporosis, 2012[32]	$14.02 B
Average expenditures on osteoporosis-related inpatient procedures and emergency room visits among all U.S. women over the age of 55 with osteoporosis, 2013–2020	$16.98 B
Cumulative hospital utilization expenditures osteoporosis-related inpatient procedures and emergency room visits among all U.S. women over the age of 55 with osteoporosis, 2013–2020	$135.81 B
Average claimed expenditures per osteoporosis-attributed fracture per person per year, 2012	$11,020
Expected average claimed expenditures per osteoporosis-attributed fracture per person per year, 2013–2020	$13,812

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

31 Includes all osteoporosis-attributed fracture treatments

32 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 outpatient or office-based provider visits, hospital inpatient stays, and emergency room visits

Calcium is the major mineral comprising bone and a key determinant in bone density. Its absorption and metabolism depend importantly on vitamin D status.

Calcium and Vitamin D

Literature Review

Calcium is the major mineral comprising bone. Its absorption and metabolism depends, in part, on vitamin D, which is converted in the kidneys to the biologically active form calcitriol (Memorial Sloan-Kettering Cancer Center, 2013) (The American Society of Health-System Pharmacists, Inc and the U.S. National Library of Medicine, 2010). Calcitriol acts as a hormone in regulating many aspects of calcium function (The American Society of Health-System Pharmacists, Inc and the U.S. National Library of Medicine, 2010). Vitamin D is naturally synthesized by humans in the skin when it is exposed to ultraviolet light. Under conditions of low light exposure, dietary sources of vitamin D are needed to maintain adequate levels (Memorial Sloan-Kettering Cancer Center, 2013). Natural sources rich in vitamin D include fatty fish, eggs, and liver (Memorial Sloan-Kettering Cancer Center, 2013). Since the 1920s, milk in the United States has been fortified with vitamin D to prevent bone disease, especially in children. In the elderly, especially among women, calcium loss from bone can result in osteoporosis, and it is associated with reduced levels of circulating vitamin D. There has been much research on dietary supplementation of calcium and vitamin D in the elderly, with the goal of minimizing osteoporosis and its complications, such as increased risk of bone fractures (Memorial Sloan-Kettering Cancer Center, 2013).

In the United States, the Food and Nutrition Board (FNB) at the IOM has established Recommended Dietary Allowances (RDA) of 1200 mg of calcium and 600 IU of vitamin D per day for women 51-70 years of age. (Institute of Medicine, 2010). The UL for calcium for adults over 50 years of age is 2000 mg. The UL for calcium was established in 2010 on the basis of data from the Women's Health Initiative relating to potential formation of kidney stones. The IOM says this value "provides a reasonable degree of public health protection without overly restricting the intake of calcium (notably from calcium supplements) for both men and women" (Institute of Medicine, 2010).

For women over the age of 70, the RDA for calcium remains 1200 mg, but the RDA for vitamin D is increased to 800 IU/day. A UL for vitamin D of 4,000 IU per day was established for all U.S. adults (NIH MedlinePlus, 2011). The UL for vitamin D was established in 2010 on the basis of the potential risk of hypercalcemia (elevated blood levels of calcium).

In order to quantify the possible effects of calcium and vitamin D supplementation in the elderly on the risk of osteoporotic fractures, a rigorous search of the literature was conducted that focused on published studies quantifying the effect of supplementation on fracture risk. The objective was to identify a set of studies that represented the state of scientific literature on a these supplements. Studies that tested for a direct causal relation between intake of the dietary supplement and the relative risk of a disease event were preferred. The research team strove to include studies that were similar to each other in protocol in an attempt to control for observable variance. Studies were not selected on the basis of the magnitude, direction or statistical significance of the reported findings.

In a rigorous search conducted on PubMed, more than 49 studies were identified by matching a combination of terms such as "calcium" and/or "vitamin D"; "osteoporosis" and/or "fracture"; and "risk reduction." A search was conducted between February 1 and May 31, 2013. Of the various reported study methods, randomized controlled trials were preferred because they are designed to directly test for a cause-and-effect relationship between supplementation and outcome. Seven RCT studies were identified as being representative of the literature, and directly tested for the relationship between dietary supplement intake and the risk of an osteoporosis-attributed bone fracture. All seven studies were of people age 50 or older—most of them were over the age of 65. In four of the studies, the subjects were women only. The RCTs compared a treatment group that received daily calcium and vitamin D supplement with a group that received a placebo. The duration of supplementation ranged from 18 months to seven years. Reported study outcomes included the incidence of various clinical fractures; Frost & Sullivan selected the change in osteoporotic fracture risk as the input for modeling the health care utilization effects of calcium and vitamin D supplementation. Four of the seven key studies are referenced and discussed in the paragraphs below. The other three are referenced in the footnotes to Figure 7.3.

Figure 7.3—Calcium and Vitamin D Literature Review: Description of the Qualified Studies

Author	Year	Event definition
Jackson	2006	all fractures (hip, clinical vertebral, lower arm, or wrist)
Chapuy	1992	non-vertebral fractures
Dawson-Hughes[33]	1997	first non-vertebral fracture
Porthouse	2005	all clinical fractures
Grant	2005	new fractures (all subjects had previous fracture)
Larsen[34]	2004	Osteoporotic fractures leading to acute hospital admission
Chapuy[35]	2002	hip fractures

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

Among the studies included was that of Chapuy (1992), the subjects of which were 3,270 healthy women in France with a median age of 86 (Chapuy, et al., 2002). The treatment group received 1.2 g of calcium and 800 IU of vitamin D per day, while the remainder received a placebo. After 18 months, the incidence of all non-vertebral fractures was 32% lower in the treatment group compared with the placebo group.

33 Dawson-Hughes, Harris, Krall, & Dallal, 1997

34 Larsen, Mosekilde, & Foldspang, 2004

35 Chapuy, et al., 2002

Jackson et al., (2006) recruited 36,282 post-menopausal women in the U.S. aged 50 to 79 years for the Women's Health Initiative (Jackson RD et al., 2006). Half received 1 gram of calcium and 400 IU of vitamin D per day, while the other half received a placebo. After an average of seven years of follow-up, the hazard ratio for all fractures in the treatment group relative to placebo group was 0.97. The risk of kidney stones was significantly higher in the treatment group. The authors noted that, during the study, a fraction of the subjects ceased to adhere to the supplementation schedule, in part because of gastrointestinal symptoms. During the first three years, 60 to 63% adhered to medication by consuming at least 80% of their supplement. By the end of the study, 59% of the subjects were taking 80% or more of their supplement. Of these women, the hazard ratio for hip fracture was 0.71, compared with 0.88 for the entire study sample, suggesting that better adherence to supplementation resulted in a lower risk of fractures.

Porthouse et al., (2005) studied 3,314 women in the U.K. over 70 years of age with one or more risk factors for fracture (Porthouse, et al., 2005). The treatment group received 1 gram of calcium and 800 IU of vitamin D per day. After a median follow-up of 25 months, the rate of fractures in the treatment group was 4.8%, versus 5.0% in the placebo group.

Grant et al., (2005) studied men and women in the U.K. over the age of 70 (Grant, et al., 2005). The treatment group received 1 gram of calcium and 800 IU of vitamin D daily. They were followed for 24 to 62 months and compared with a placebo group. The rate of all new fractures in the treatment group was 14.1%, compared with 14.7% in the placebo group.

Dawson-Hughes et al., (1997) conducted a randomized placebo-controlled trial of 389 men and women in the U.S. over the age of 65. The treatment group received 500 mg of calcium and 700 IU of vitamin D daily; while the remainder received placebo. After three years the incidence of a first fracture was 5.9% in the treatment group and 12.9% in the placebo group.

Larsen et al., (2004) in Denmark studied men and women age 66 and over. The treatment group of 4,957 received 1 gram of calcium and 400 IU of vitamin D daily, while the control group of 2,116 received no intervention. After 42 months the relative risk of osteoporotic fractures was 0.81 for the treatment group compared to the group with no intervention.

Chapuy et al., (2002) conducted a placebo-controlled randomized study of 583 institutionalized women in France of average age 85 years. The treatment group received 1.2 grams of calcium and 800 IU of vitamin D daily. After 2 years the relative risk of hip fracture in the treatment group compared to the placebo group was 0.59.

Figure 7.4—Calcium and Vitamin D Literature Review: Description of the Qualified Studies

Author	Total sample (N)	Relative risk (RR)	Study weight based on within study and between study variance
Jackson	36,282	0.97	22.55%
Chapuy (1992)	3,270	0.75	16.62%
Dawson-Hughes	389	0.46	6.15%
Porthouse	3,314	0.96	19.89%
Grant	2,638	0.96	14.49%
Larsen	7,073	0.81	20.30%
Chapuy (2002)	583	0.59	23.40%

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

An average of 151,053 avoided osteoporosis-attributed bone fractures per year from 2013 to 2020 or 1.2 million accumulated avoided osteoporosis-attributed bone fractures over the same period is realizable if all U.S. women over the age of 55 diagnosed with osteoporosis were to use calcium and vitamin D dietary supplements to achieve daily protective intake levels.

Empirical Results

Using the D-L approach (DerSimonian & Laird, 1986), the estimated relative risk reduction of a osteoporosis-related medical event (specifically osteoporosis-attributed fractures) given the use of calcium and vitamin D dietary supplements at preventive daily intake levels, was 18.6% after controlling for variance because of sample size, research methodologies and study protocols, and patient population differences within each study and among all studies. Using the D-L approach to calculate the NNT, it was determined that 58 people had to be treated with calcium and vitamin D supplements to avoid one osteoporosis-attributed fracture event.

Figure 7.5—Calcium and Vitamin D Literature Review: Summary Results—D-L Approach

Metric	Measure
Weighted relative risk (weighted for intra-study variance), (RR)	81.4%
Weighted relative risk reduction (weighted for intra-study variance), (RRR)	18.6%
Number of people needed to be treated to avoid one osteoporosis-attributed fracture (NNT), people	58
Average number of fractures avoided annually if everybody in the target population* used calcium and vitamin D supplements to achieve protective intake levels , 2013–2020, people	151,053
Cumulative number of fractures avoided if everybody in the target population* used calcium and vitamin D supplements to achieve protective intake levels, 2013–2020, people	1,208,422

*All women over the age of 55 with osteoporosis
Note: All figures are rounded. Source: Frost & Sullivan

An average of $1.87 billion per year and a cumulative savings of $15.00 billion from 2013 to 2020 in avoidable hospital utilization costs is potentially realizable if all U.S. women over the age of 55 diagnosed with osteoporosis were to use calcium and vitamin D dietary supplements at preventive daily intake levels.

Given the estimated NNT of 58 people, the effect on avoided hospital utilization expenditures related to osteoporosis-attributed fractures among all U.S. women over the age of 55 would be an average annual total savings of $1.8 billion per year and cumulative savings of $15 billion from 2013 to 2020, assuming an average annual per person cost of an event at $11,020. This equates to an average of 151,053 avoided events per year over the next seven years or 1,208,422 accumulated avoided events over the same period.

A review of the retail calcium and vitamin D products on the market revealed that the cost of a daily dose of calcium and vitamin D ranges from $0.06 to $0.32. The median cost is $0.16 per day. Using this figure, the expected annual cost of supplementation for each woman over the age of 55 with diagnosed osteoporosis would be $43.22, for a total of more than $356 million per year for the entire subpopulation—more than $2.8 billion cumulatively from 2013 to 2020. The net cost savings, after accounting for the cost of calcium and vitamin D dietary supplementation, would average $1.5 million per year—$12.15 billion cumulatively from 2013 to 2020. See Figures 8.26 to 8.29 in the appendix for a detailed reporting of the empirical results.

Figure 7.6—Calcium and Vitamin D Cost Analysis: Summary Results—Cost of Dietary Supplementation of the Target Population*, 2013–2020

Metric	Measure
Median cost of calcium and vitamin D supplementation at protective daily intake levels, 2013	$0.16
Expected annual median cost of calcium and vitamin D supplementation at protective daily intake levels, 2013	$43.22
Average annual cost of calcium and vitamin D dietary supplementation of the target population, 2013–2020	$355.8 M
Cumulative cost of calcium and vitamin D dietary supplementation of the target population, 2013–2020	$2.85 B

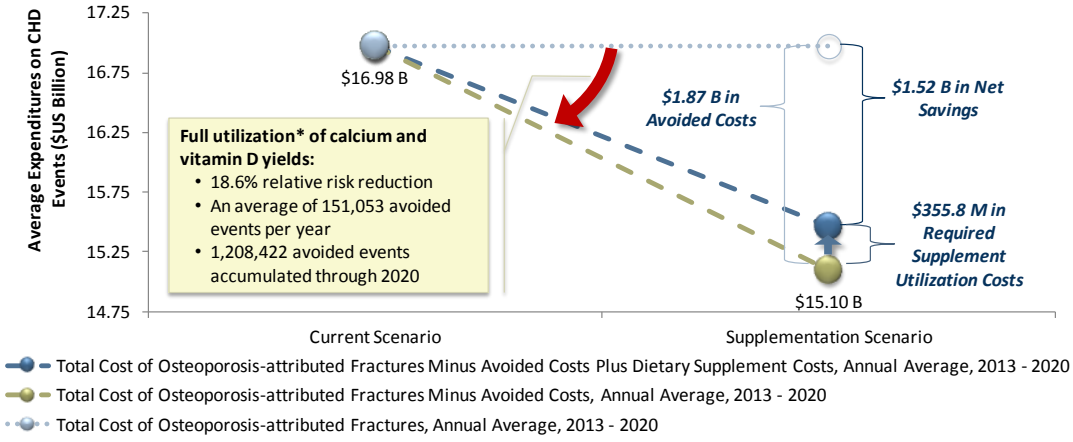
*Among all U.S. women over the age of 55 with osteoporosis
Note: All figures are rounded. Source: Frost & Sullivan

Figure 7.7—Calcium and Vitamin D 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 osteoporosis-attributed fractures among the target population* if incidence is reduced through the use of calcium and vitamin D supplements, 2013–2020	$1.87 B
Cumulative avoided hospital utilization expenditures related to osteoporosis-attributed fractures among the target population* if incidence is reduced through the use of calcium and vitamin D supplements, 2013–2020	$15.00 B
Average annual hospital utilization expenditures osteoporosis-attributed fractures among the target population* if incidence is reduced through the use of calcium and vitamin D supplements, 2013–2020	$15.10 B
Cumulative hospital utilization expenditures osteoporosis-attributed fractures among the target population* if incidence is reduced through the use of calcium and vitamin D supplements, 2013–2020	$120.81 B

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

Figure 7.8—Calcium and Vitamin D Cost Analysis: Net Health Care Cost Savings* Summary Results, 2013–2020



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

Figure 7.9—Calcium and Vitamin D 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 osteoporosis-attributed fractures due to calcium and vitamin D dietary supplement intervention, 2013–2020	$1.52 B
Cumulative net potential direct savings from avoided osteoporosis-attributed fractures due to calcium and vitamin D dietary supplement intervention, 2013–2020	$12.15 B
Net benefit cost ratio, $ per one dollar spent on dietary supplement	$5.27

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

The prior cost-benefit analysis assumes that in the supplementation scenario all U.S. women over the age of 55 with osteoporosis use calcium and vitamin D 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 that are realizable. However, because a significant proportion of women over the age of 55 with osteoporosis are regular users of calcium and vitamin D dietary supplements, this segment of the target population already has a reduced risk of experiencing a costly osteoporosis-attributed fracture and is realizing the supplements' risk-reducing benefits.

Over $12 billion in cumulative net osteoporosis-attributed cost savings is potentially realizable if the entire target population were to use calcium and vitamin D dietary supplements at protective daily intake levels.

It is expected that there are significant potential cost savings yet to be realized valued at over $8.6 billion in cumulative net osteoporosis-attributed cost savings if all current non-regular users in the high-risk target population were to fully utilize calcium and vitamin D dietary supplements at protective intake levels from 2013 to 2020.

According to the 2012 Council for Responsible Nutrition Consumer Survey on Dietary Supplements conducted by Ipsos Public Affairs and Frost & Sullivan estimates, 29% of women over the age of 55 in the United States are regular users of calcium and vitamin D dietary supplements (Ipsos Public Affairs, 2012).[36] This implies that 71% do not realize the benefits of regular usage. Because avoided expenditures and net cost savings are a direct function of the total number of people in the target population using calcium and vitamin D 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.

Knowing this, it is expected that more than $440.0 million of the $1.52 billion in net potential direct savings per year from avoided osteoporosis-attributed fractures due to calcium and vitamin D dietary supplement intervention is already realized in the total expected costs. This equates to an average of 107,248 avoidable events per year yet to be realized because of underutilization of these supplements, which corresponds to an average of $1.08 billion per year in net savings yet to be realized—nearly $8.63 billion in cumulative net savings from 2013 to 2020. Thus, it is expected that there is significant cost savings yet be realized through the increased usage of calcium and vitamin D dietary supplements among the high-risk target population.

Figure 7.10—Calcium and Vitamin D 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 women over the age of 55 who are regular users of calcium and vitamin D dietary supplements, 2012	29%
Average number of events avoided annually among the target population* yet to regularly use calcium and vitamin D supplements, 2013–2020	107,248
Cumulative number of events avoided among the target population* yet to regularly use calcium and vitamin D supplements, 2013–2020	857,980
Average net direct savings per year from avoided osteoporosis-attributed fractures due to calcium and vitamin D dietary supplement intervention yet to be realized, 2013–2020	$1.08 B
Cumulative net direct savings from avoided osteoporosis-attributed fractures due to calcium and vitamin D dietary supplement intervention yet to be realized, 2013–2020	$8.63 B

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

36 It is not known what percentage of this target population also suffers from osteoporosis, but for the purposes of this analysis, Frost & Sullivan has made the assumption that approximately the same percentage—33% and 29%—of women over the age of 55 regularly takes calcium supplements and vitamin D supplements, respectively. Further, Frost & Sullivan took the lower of the two percentages—vitamin D at 29%—since it is necessary to realize a preventive effect. Finally, 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 calcium and vitamin D to provide a protective effect. More research is required to test these assumptions.

Magnesium

Magnesium is a key structural constituent of bone.

Literature Review

About 60% of all magnesium in the body is found in bone, where it is a structural constituent, along with calcium phosphate; this magnesium makes up about 1% of the total bone mineral content (Memorial Sloan-Kettering Cancer Center, 2013). Major dietary sources of magnesium are leafy green vegetables, such as spinach; wheat bran and whole grains; nuts; and legumes, such as lentils and black-eyed peas (Memorial Sloan-Kettering Cancer Center, 2013).

The IOM recommends that women over the age of 31 consume 320 mg of magnesium per day (Memorial Sloan-Kettering Cancer Center, 2013). No UL has been established for magnesium consumed in foods because there are no reports of adverse effects from consuming magnesium through food; however, consumption of magnesium in a concentrated source, such as a tablet, can potentially have a laxative effect. Because of this, the IOM in 1997 established a UL of 350 mg for supplementary magnesium based on the potential for diarrhea from the use of supplemental or pharmacologic magnesium salts. A LOAEL of 360 mg for supplemental or pharmacologic magnesium sources was established, and an uncertainty factor close to 1 was applied to derive the UL of 350 mg. The low uncertainty factor was selected "due to the very mild, reversible nature of osmotic diarrhea caused by ingestion of magnesium salts" (Institute of Medicine, 1997).

For the purpose of modeling magnesium supplementation for health care, this analysis focused only on the risk of fractures attributed to osteoporosis. The objective was to identify a set of studies that represented the state of scientific literature on magnesium supplementation and its link to fracture risk. The only available studies that looked at this subject tested for a causal relationship between magnesium supplement intake and the level of bone density, which is correlated to the relative risk of fracture. The research team only included studies similar in protocol in an attempt to control for observable variance. Studies were not selected on the basis of the magnitude or statistical significance of the reported findings.

Through a rigorous search conducted on PubMed, 12 studies were identified as matching keyword combinations such as "magnesium"; "osteoporosis" and/or "fracture"; and "risk reduction." The search was conducted between February 1 and May 31, 2013. Initially, the search focused on studies that directly linked magnesium supplementation to fracture risk in women because of their greater risk of fractures related to bone health; however, no such studies were identified. The search then expanded for studies relating magnesium dietary intake and its relation to bone mineral density (BMD). The research team's search identified two representative epidemiological studies of dietary magnesium intake and BMD.

In a prospective study, Tucker et al., (1999) questioned 562 elderly U.S. women about dietary intake over one year (Tucker, Hannan, Chen, Cupples, Wilson, & Kiel, 1999). BMD was measured by dual photon absorptiometry (DPA) at three sites in the hip (femoral neck, trochanter, and Ward's area) and one site in the forearm (radius). The authors found that for every 100 mg increase in magnesium intake, BMD was significantly higher in the hip, by 0.02 g/cm2 in the trochanter and by 0.016 g/cm2 in Ward's area. The increase at the femoral neck was 0.012 g/cm2, but this was not statistically significant.

Ryder et al., (2005) prospectively studied black and white men and women in the U.S. between the ages of 70 and 79. Subjects were questioned on dietary variables, and BMD was measured by whole body dual energy X-ray absorptiometry (DXA) (Ryder, et al., 2005). In white women (n=534), magnesium intake was positively associated with increased BMD. The difference in BMD between the highest and lowest quintile of magnesium intake was 0.04 g/cm2. This relationship was not statistically significant in black women.

To estimate changes in fracture risk from changes in bone mineral density because of magnesium intake, the FRAX online tool (WHO Fracture Risk Assessment Tool) was employed (World Health Organization Collaborating Centre for Metabolic Bone Diseases, 2013). This tool takes inputs factors such as sex, age, height, weight, and BMD at the femoral neck. The FRAX outputs are 10-year probabilities for the following: (a) major osteoporotic fracture; and (b) hip fracture.

To model fracture risk with FRAX, Frost & Sullivan used the following input factors:

- Female
- 70 years of age, average
- 63 inches in height, average
- 140 pounds in weight, average
- Bone densitometry system: GE Lunar

The resulting calculated input value for BMD was 0.700 g/cm2, which is near the upper limit of the definition of osteoporosis (World Health Organization Collaborating Centre for Metabolic Bone Diseases, 2013). These inputs yielded a specific fracture risk from the FRAX tool. Frost & Sullivan then repeated the calculation to obtain a fracture risk using a BMD of 0.688 g/cm2. The difference between the two BMD values is 0.012 g/cm2. Tucker et al., (1999) found that a 100 mg/day increase in magnesium intake is correlated with an increase in BMD of 0.012 g/cm2 at the femoral neck. Frost & Sullivan chose to model a 100 mg/day increase in magnesium, noting that 100 mg/day is approximately one standard deviation of the mean magnesium intake in the study of Tucker et al., (Tucker, Hannan, Chen, Cupples, Wilson, & Kiel, 1999).

Having values of fracture risk for each of the two BMD values, Frost & Sullivan next calculated the relative risk at 0.700 g/cm2 compared with 0.688 g/cm2 and obtained a value of 0.93 relative risk. This process for calculating relative risk was repeated with inputs for a woman 80 years of age. In this case, the relative risk was 0.95. The average of these two (0.94) is the relative risk used as input for economic modeling, assuming a magnesium intake of 100 mg/day more than normal intake levels.

Empirical Results

The calculated relative risk reduction of an osteoporosis-related medical event, specifically osteoporosis-attributed fractures, given the use of magnesium dietary supplements at the preventive level of 100 mg per day, was 6% after controlling for variance due to sample size, research methodologies and study protocols, and patient population differences within each study and among all studies. Given that 1.3 million women over the age of 55 will experience an osteoporosis-related fracture out of the 8.2 million people who are classified as high-risk (15.1% of the total sub-population), using the CEBM approach, 129 people must use magnesium supplements at the preventive level of 100 mg per day to avoid one osteoporosis-attributed fracture.

An average of 68,536 avoided osteoporosis-attributed bone fractures per year from 2013 to 2020 or 548,284 accumulated avoided osteoporosis-attributed bone fractures over the same period is realizable if all U.S. women over the age of 55 diagnosed with osteoporosis were to use magnesium dietary supplements at the preventive intake level of 100 mg per day.

Figure 7.11—Magnesium Literature Review: Overall Results—CEBM Approach

Metric	Measure
Weighted relative risk (weighted for intra-study variance)	94.0%
Weighted relative risk reduction (weighted for intra-study variance)	6.0%
Number of people needed to be treated to avoid one osteoporosis-attributed fracture event (NNT), people	129
Average number of fractures avoided annually if everybody in the target population* used magnesium supplements at the preventive intake level of 100 mg per day, 2013–2020, people	68,536
Cumulative number of fractures avoided if everybody in the target population used magnesium supplements at the preventive intake level of 100 mg per day, 2013–2020, people	548,284

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

Given the NNT of 129 people, which is achievable if every individual high-risk in the target population—all U.S. women over the age of 55 with osteoporosis—were to take magnesium supplements at the preventive intake level of 100 mg per day, the effect on avoided expenditures related to osteoporosis-attributed fractures would be an average annual total savings of up to $851 million per year and cumulative savings of $6.8 billion from 2013 to 2020. This equates to an annual average of 68,536 avoided events over the next seven years and 548,284 accumulated avoided events over the same period.

An average of $850.6 million per year and a cumulative savings of $6.80 billion from 2013 to 2020 in avoidable hospital utilization costs is potentially realizable if all U.S. women over the age of 55 diagnosed with osteoporosis were to use magnesium dietary supplements at the preventive intake level of 100 mg per day.

Based on the review of best-selling magnesium supplement products in leading brick-and-mortar, online, and mail-order retail establishments, the cost of a daily dose of magnesium is between $0.03 and $0.34. The median daily price is $0.085—$31.01 per year. Given this median price, the total expected average annual cost of supplementation for 8.2 million people would be $255.3 million per year and $2.04 billion in cumulative expenditures from 2013 to 2020.

Figure 7.12—Magnesium Cost Analysis: Summary Results—Cost of Dietary Supplementation of the Target Population*, 2013–2020

Metric	Measure
Median cost of magnesium supplementation at protective levels, 2013	$0.09
Expected annual median cost of magnesium supplementation at protective levels, 2013	$31.01
Average annual cost of magnesium dietary supplementation of the target population* , 2013–2020	$255.3 M
Cumulative cost of magnesium dietary supplementation of the target population* , 2013–2020	$2.04 B

*All women over the age of 55 with osteoporosis
Note: All figures are rounded. Source: Frost & Sullivan

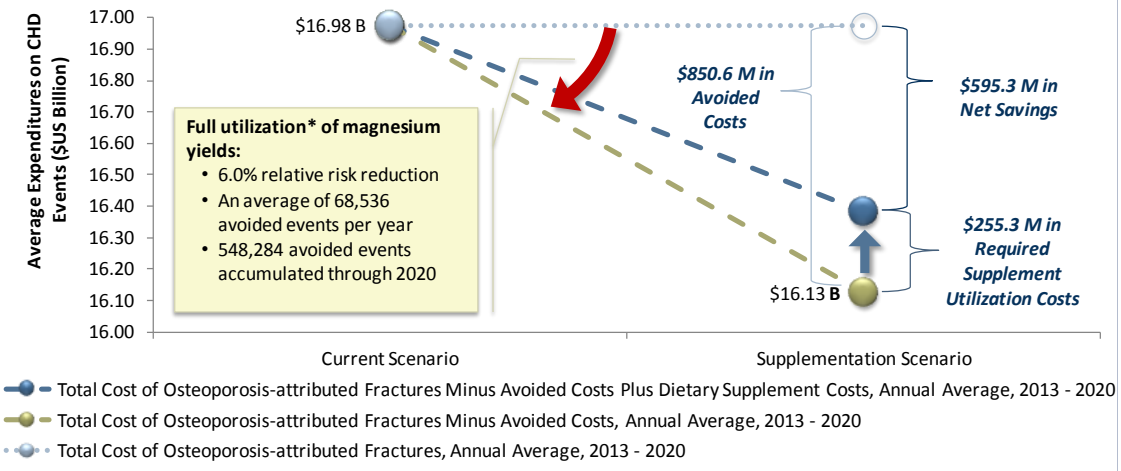
Figure 7.13—Magnesium Cost Analysis: Summary Results—Avoided Hospital Utilization Expenditures* due to Dietary Supplement Intervention, 2013–2020

Metric	Measure
Average annual avoided hospital utilization expenditures related to osteoporosis-attributed fractures among the target population* if incidence is reduced through the use of magnesium supplements, 2013–2020	$850.6 M
Cumulative avoided hospital utilization expenditures related to osteoporosis-attributed fractures among the target population* if incidence is reduced through the use of magnesium supplements, 2013–2020	$6.80 B
Average annual hospital utilization expenditures osteoporosis-attributed fractures among the target population* if incidence is reduced through the use of magnesium supplements, 2013–2020	$16.13 B
Cumulative hospital utilization expenditures osteoporosis-attributed fractures among the target population* if incidence is reduced through the use of magnesium supplements, 2013–2020	$129.00 B

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

Thus, the total hospital utilization cost savings derived from avoided osteoporosis events for the same population was, on average, $851 million per year and nearly $6.8 billion in cumulative savings during the forecast period. The net savings, after accounting for the cost of magnesium dietary supplementation, would average $595.3 million per year and total $4.76 billion from 2013 to 2020. See Figures 8.30 to 8.33 in the appendix for a detailed reporting of the empirical results.

Figure 7.14—Magnesium Cost Analysis: Net Health Care Cost Savings* Summary Results, 2013–2020



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

Figure 7.15—Magnesium 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 osteoporosis-attributed fractures among the target population* due to magnesium dietary supplement intervention, 2013–2020	$595.3 M
Cumulative net potential direct savings from avoided osteoporosis-attributed fractures among the target population* due to magnesium dietary supplement intervention, 2013–2020	$4.76 B
Net benefit cost ratio, $ per one dollar spent on dietary supplement	$3.33

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

This cost-benefit analysis assumes that in the supplementation scenario all U.S. women over the age of 55 with osteoporosis use magnesium dietary supplements from a base of zero use among this population segment. In other words, the calculated net savings is actually the total potential net savings that are realizable. However, because some women over the age of 55 with osteoporosis are already regular users of magnesium dietary supplements, this segment of the target population has a reduced risk of experiencing a costly osteoporosis-attributed fracture and is realizing the supplement's risk-reducing benefits.

$4.76 billion in cumulative net osteoporosis-attributed cost savings is potentially realizable if the entire target population were to use magnesium dietary supplements to increase intake by 100 mg per day.

It is expected that there are significant potential cost savings yet to be realized valued at nearly $4.24 billion in cumulative net osteoporosis-attributed cost savings if all current non-regular users in the high-risk target population were to utilize magnesium dietary supplements at the preventive intake level of 100 mg per day.

According to the 2012 Council for Responsible Nutrition Consumer Survey on Dietary Supplements conducted by Ipsos Public Affairs and Frost & Sullivan estimates, 11% of U.S. women over the age of 55 are regular users of magnesium dietary supplements (Ipsos Public Affairs, 2012).[37] This implies that 89% do not realize the benefits of regular magnesium supplement usage. Because avoided expenditures and net cost savings are a direct function of the total number of people in the target population using magnesium 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.

It is estimated that more than $65.5 million of the $595.3 million in net potential direct savings per year from avoided osteoporosis-attributed fractures because of magnesium dietary supplementation is already realized. This equates to an average of 60,997 avoidable events per year yet to be realized due to underutilization of magnesium supplements, which corresponds to an annual average of $529.8 M per year in net savings yet to be realized due to underutilization of magnesium dietary supplements or nearly $4.24 B in cumulative net savings from 2013 to 2020. Thus, it is expected that there is significant cost savings yet to be realized through the increased usage of magnesium dietary supplements among the high-risk target population.

37 It is not known what percentage of this target population also suffers from osteoporosis, but for the purposes of this analysis, Frost & Sullivan has made the assumption that approximately the same percentage—11%—of women over the age of 55 regularly takes magnesium 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 magnesium supplements to provide a protective effect. More research is required to test these assumptions.

Figure 7.16—Magnesium 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 women over the age of 55 who are regular users of magnesium dietary supplements, 2012	11%
Average number of events avoided annually among the target population* yet to regularly use magnesium supplements ,2013–2020	60,997
Cumulative number of events avoided among the target population* yet to regularly use magnesium supplements, 2013–2020	487,973
Average net direct savings per year from avoided osteoporosis-attributed fractures among the target population* due to magnesium dietary supplement intervention yet to be realized, 2013–2020	$529.8 M
Cumulative net direct savings from avoided osteoporosis-attributed fractures among the target population* due to magnesium dietary supplement intervention yet to be realized, 2013–2020	$4.24 B

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

Conclusion

Osteoporosis is the most prevalent bone disease in the United States, with more than $14.00 billion in annual direct health care costs for treatment of osteoporosis fractures. This cost does not include post-procedure care, loss of mobility and independence, and a general reduction in a patient's quality of life. Given the full usage of calcium and vitamin D at preventive daily intake levels among all U.S. women over the age of 55 diagnosed with osteoporosis, upwards of $1.5 billion per year and more than $12.20 billion from 2013 to 2020 can be saved because of avoided osteoporosis-attributed fractures. This equates to $5.27 in savings per $1 spent on calcium and vitamin D supplements. For magnesium dietary supplementation, the total net cost savings from avoided osteoporosis events among the same high-risk population would average $595.3 million per year and over $4.8 billion in cumulative health care cost savings over the next seven years could be realized from 2013 to 2010, or $3.33 per $1 spent on magnesium supplements. As fractures attributed to osteoporosis become more prevalent in the U.S. due to the general aging of America, the importance of leveraging the substantiated benefits of calcium, vitamin D, and magnesium to help prevent costly events is an obvious means to help control the increasing financial burden of this disease.

As fractures attributed to osteoporosis become more prevalent in the U.S. due to the general aging of America, the importance of leveraging the substantiated benefits of calcium, vitamin D, and magnesium as a means to help prevent these costly events is an obvious means to help control the increasing financial burden of this disease.

APPENDIX

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Literature Review Methodology

DerSimonian and Laird (D-L) Random-effects Literature Review Methodology

For this study, a random-effects literature review model was adopted for use in cases where the dietary supplement in question had a significant number of scientific/clinical studies that explored the specific question this study aims to address: What is the impact on the odds of a disease event occurring, given the use of the dietary supplement in question? This question is in the same mold of many questions that pharmacoeconomic/clinical studies aim to address, which is the determination of an overall treatment effect on a given event outcome when a treatment regimen is applied to one group versus a control group. From these type of analyses, risk—and, subsequently, risk reduction—of an event can be calculated and applied into a cost-effectiveness model, which helps key decision makers (including physicians, patients, governments, insurance companies, and employers) determine whether it is worth the increased cost of treatment for the potential savings derived from avoided events.

However, the key problem is how one properly assesses the results of a set of studies, which we define as ***K***, that address the same research question, when each study (element of set ***K*** = study ***i***) varies significantly in terms of sample size, study protocol, the research team, and a host of other study qualities. Researchers, specifically DerSimonian and Laird (DerSimonian & Laird, 1986, DerSimonian & Kacker, 2007), have addressed this critical issue over the last several decades, and the research consensus has determined that the random-effects model is one of the best approaches available to researchers when key quality variables are unknown.

The random-effects model assumes that the observed effect of a treatment in a given study ***i***, Y_i is a function of two components, the overall effect of treatment, Y_i^*, and a sampling error in study ***i***, ε_i. It is assumed that the functional relationship is linear, or

- $Y_i = Y_i^* + \varepsilon_i$.

Sampling error can be caused by many factors internal to the given study, such as inadvertently selecting a biased sample from the population, but it mostly due to the relative size of the study sample, N_i. The sampling error also provides insight into the precision of the findings—the larger the error, the more likely the findings are less precise and, consequently, the lower the confidence one should have in the results when compared with another study's results, if that study has a smaller sampling error.

Sampling error is not the only variance that must be considered when assessing a set of studies. The true effect of treatment, Y_i^*, can also vary based on many factors, such as the dosage size of treatment, the demographics of the population receiving the treatment, the study's methodology, and/or protocol that impacts the treatment's effect. All of these true treatment effects vary by study and must be accounted for in order to understand the true treatment effect on the total population. Thus, equation (1) must be transformed to account for intra-study variance, thus

- $Y_i = \mu^* + \delta_i + \varepsilon_i$

Where μ^* is the true treatment's effect on a given population independent of the studies and δ_i is the difference in study ***i***'s observed effect from the true treatment's effect on a given population, or intra-study error.

Thus, the goal is to provide an estimate of μ^*, by controlling for δ_i and ε_i, which is done through a weighting process where the weights are functions of the variance in inter-study error (ε_i), defined as s_i^2, and the variance in intra-study error (δ_i), defined as τ^2. In other words, each study's observed treatment effect is adjusted using the following equation:

- $X = (\Sigma_i w_i * Y_i) / \Sigma_i w_i$
- $w_i = (s_i^2 + \tau^2)^{1/2}$

Where ***X*** is the deduced treatment effect that is used in the cost-saving calculations and $\mathbf{w_i}$ is the variance weight applied to each study to control for inter-study and intra-study variance in the observed treatment effect of each study **i**.

Various approaches to calculating s_i^2 and τ^2 which are sufficiently outlined by many prior studies, including the work of DerSimonian and Kacker (2007); however, for the purposes of this study, the two-step DerSimonian and Laird was adopted to calculate s_i^2, τ^2, and ***X***.

Center for Evidence Based Medicine (CEBM) Approach—Estimated Number needed to be Treated Function Calculation

In cases where the use of the random effects model is not appropriate, such as the case when the number of qualified studies is small or when the relationship between the supplement intervention's effect and the utilization of costly treatment services is indirect, a much simpler, though less accurate, estimation function that determines the number needed to be treated was used. In these cases, all that is needed for the function is an average relative risk reduction or the odds ratio and the current disease incidence rate (Center for Evidence Based Medicine, 2012).

As stated, the number needed to treat (NNT) is the total number of people that would have to undergo a treatment intervention to realize one avoided undesired event. For example, if it was found that a given dietary supplement had a NNT of 100, this would mean that 100 people would have to be treated in order to avoid one undesired event from occurring in the same population. In order to calculate an estimate of the NNT from just knowing the current incidence rate and the expected odds ratio and/or relative risk reduction metric, the following function should be calculated:

- $NNT = (1-(ER*(1-RRR))) / ((1-ER)*(ER)*(1-RRR))$

Where ER is the event or disease event incident rate among the high-risk population and the RRR is the estimated relative risk reduction and/or the odds ratio.

List of Common Variables and Equations Health Economics Research

- Total sample size per study = **N**
- Number of events occurring in the treatment group per study = **EE**
- Number of events occurring in the control group per study = **CE**
- Observed event rate (observed disease prevalence in the target population) = **ER**
- Treatment group event rate—**TER = EE / N**
- Control group event rate—**CER = CE / N**
- Relative risk—**RR = TER/CER**
- Absolute risk reduction—**ARR = CER – TER**
- Relative risk reduction—**RRR = ARR/CER**
- Number needed to treat—**NNT = 1/ARR = CER/RRR**
- Number needed to treat using the CEBM approach (only requires the use of the observed event rate and the deduced relative risk reduction) = **(1-(ER*(1-RRR))) / ((1-ER)*(ER)*(1-RRR))**

List of Abbreviations

AMD	Age-related macular degeneration
AOA	American Optometric Association
ARED	Age-related eye disease
B	billion
B12	Vitamin B - cyanocobalamin
B6	Vitamin B - pyridoxine
B9	Vitamin B - folate
BMD	Bone mineral density
CBA	Cost-benefit analysis
CDC	Center of Disease Control and Prevention
CHD	Coronary heart disease
CI	Confidence interval
CTT	Cholesterol Treatment Trialists
DHA	Docosahexaenoic acid
DPA	Dual photon absorptiometry
DSHEA	Dietary Supplement Health and Education Act
DXA	Dual energy X-ray absorptiometry
EPA	Eicosapentaenoic acid
ER	Event or disease event incident rate among the high-risk population
FNB	Food and Nutrition Board
FRAX	Fracture Risk Assessment Tool
g	gram
HbA1c	Glycated hemoglobin
IOM	The Institute of Medicine
IU	International unit
LDL	Low-density lipoprotein
M	million
mcg	microgram
MEPS	Medical Expenditure Panel Survey
mg	milligram
mg/dL	milligrams per deciliter
MI	Myocardial infarction
mmol/L	millimoles per liter
NAS	National Academy of Sciences
NCEP	National Cholesterol Education Program
NNT	Number needed to treat
OR	Odds ratio
PUFA	Polyunsaturated fatty acids
RCT	Randomized controlled trials
RRR	Relative risk reduction
UL	Tolerable Upper Intake Level

Detailed Figures

Omega-3 and CHD Analysis

Figure 8.1—Omega-3 and Coronary Heart Disease Cost Analysis for All U.S. Adults over the Age of 55, 2013–2020

Year	Number of adults over the age of 55 with CHD (people)	Expected number of adults over the age of 55 with CHD who will experience a new CHD-related hospitalization event (people)	Mean CHD expenditure per person experiencing a CHD event ($)	Total CHD event expenditure among all U.S. adults over the age of 55* ($)	Total CHD event expenditure among all U.S. adults over the age of 55 given omega-3 intervention at preventive daily intake levels* ($)	Change in CHD expenditure among all U.S. adults over the age of 55 given omega-3 intervention at preventive daily intake levels (avoided costs = benefits)* ($)
2013	17,256,590	4,899,840	$13,982.49	$68,511,963,964	$66,702,608,126	**$1,809,355,838**
2014	17,515,439	4,973,338	$14,681.61	$70,889,927,762	$69,017,771,467	**$1,872,156,295**
2015	17,789,118	5,051,046	$15,415.69	$73,395,594,202	$71,457,264,906	**$1,938,329,296**
2016	18,089,309	5,136,283	$16,186.48	$76,083,351,550	$74,074,040,353	**$2,009,311,197**
2017	18,405,872	5,226,168	$16,995.80	$78,918,010,400	$76,833,837,731	**$2,084,172,669**
2018	18,739,479	5,320,892	$17,845.59	$81,908,562,433	$79,745,411,254	**$2,163,151,179**
2019	19,102,556	5,423,984	$18,737.87	$85,116,813,467	$82,868,934,492	**$2,247,878,975**
2020	19,484,607	5,532,464	$19,674.77	$88,504,958,469	$86,167,600,816	**$2,337,357,653**
Cumulative, 2013–2020	--	--	--	$623,329,182,248	$606,867,469,145	**$16,461,713,103**
Average, 2013–2020	**18,297,871**	**5,195,502**	**$16,690**	**$77,916,147,781**	**$75,858,433,643**	**$2,057,714,138**

* Discounted at a 3% rate to show present value

Source: Summary Health Statistics for U.S. Adults: National Health Interview Survey 2011, Centers for Disease Control and Prevention and Frost & Sullivan

Figure 8.2—Omega-3 and Coronary Heart Disease, Number of Avoided CHD Events Given Use of Omega-3 for All U.S. Adults over the Age of 55, 2013–2020

Year	Number of avoided events (events)
2013	129,402
2014	131,343
2015	133,395
2016	135,646
2017	138,020
2018	140,521
2019	143,244
2020	146,109
Cumulative, 2013–2020	**1,097,678**
Average, 2013–2020	**137,210**

Source: Summary Health Statistics for U.S. Adults: National Health Interview Survey 2011, Centers for Disease Control and Prevention and Frost & Sullivan

Figure 8.3—Omega-3 Retail Prices of Best-selling Brands, 2013

Best-selling brands	Number of caps per daily intake (1000 mg of EPA + DHA)	Price per daily dose ($)	Annual cost of supplement utilization per person ($)
GNC Triple Strength Fish Oil 1500	1	$0.38	$139.95
Now Foods, Omega-3, Cardiovascular Support, 200 Softgel	2	$0.08	$30.24
Natural Factors, RxOmega-3 Factors, EPA 400 mg/DHA 200 mg, 240 Softgels	2	$0.25	$91.22
Madre Labs, Omega-3 Premium Fish Oil, 180 mg EPA/120 mg DHA, 100 Softgels	2	$0.10	$36.16
Carlson Labs, Super Omega·3 Gems, Fish Oil Concentrate, 1000 mg, 100 Soft Gels + 30 Free Soft Gels	2	$0.27	$100.30
Nordic Naturals, Ultimate Omega, Lemon Flavor, 1000 mg, 180 Soft Gels	2	$0.66	$241.31
Puritan's Pride - Double Strength Omega-3 Fish Oil 1200mg	2	$0.17	$60.83
Vitamin Shoppe - Omega 3 Fish Oil 600 EPA / 240 DHA	1	$0.09	$33.47
Carlson Laboratories - Super Omega-3 Fish Oil	3	$0.12	$43.79
Carlson Laboratories - The Very Finest Fish Oil Lemon Flavor	2	$0.47	$170.33
Nordic Naturals - Ultimate Omega	1	$0.17	$60.81
the Vitamin Shoppe - Omega 3 Fish Oil 300 EPA / 200 DHA	2	$0.36	$130.39
Barlean's Organic Oils - Fish Oil	1	$0.34	$124.15
Country Life - Omega-3 Fish Body Oils	1	$0.33	$120.65
Twinlab - Mega Twin EPA	2	$0.32	$116.81
Vitacost Mega EFA® Omega-3 EPA & DHA Fish Oil -- 2,126 mg per serving - 240 Softgels	2	$0.17	$62.79
Omega-3 Fish Oil 1000 mg., 250 Softgels	3	$0.22	$82.13
Triple Strength Omega-3 Fish Oil 1360 mg, 180 Softgels	1	$0.26	$94.30
Nature Made Ultra Omega-3 Mini Fish Oil 500 mg Liquid Softgels	3	$0.25	$93.08
Windmill Natural Omega 3 EPA+DHA Fish Oil Concentrate 1000mg Dietary Supplement Softgels	1	$0.16	$59.84
GNC Triple Strength Fish Oil 1500	1	$0.38	$139.95
	Median Price	$0.25	$92.15

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

Figure 8.4—Omega-3 and Coronary Heart Disease Cost Analysis for All U.S. Adults over the Age of 55, 2013–2020

Year	Change in CHD expenditure among all U.S. adults over the age of 55 given omega-3 intervention at preventive daily intake levels (avoided costs = benefits)* ($)	Expected per person cost of omega-3 at preventive annual intake levels ($)	Expected cost of dietary supplementation of among all U.S. adults over the age of 55 with CHD at preventive daily intake levels* (supplement utilization costs) ($)	Net cost savings derived from avoided CHD events given required omega-3 dietary supplement expenditures among all U.S. adults over the age of 55, 2013–2020 ($)
2013	$1,809,355,838	$92.15	$1,590,186,704	**$219,169,133**
2014	$1,872,156,295	$93.07	$1,582,698,932	**$289,457,364**
2015	$1,938,329,296	$94.00	$1,576,216,397	**$362,112,899**
2016	$2,009,311,197	$94.94	$1,571,692,426	**$437,618,771**
2017	$2,084,172,669	$95.89	$1,568,144,674	**$516,027,996**
2018	$2,163,151,179	$96.85	$1,565,565,989	**$597,585,190**
2019	$2,247,878,975	$97.82	$1,564,910,503	**$682,968,472**
2020	$2,337,357,653	$98.80	$1,565,214,370	**$772,143,283**
Cumulative, 2013–2020	$16,461,713,103	--	$12,584,629,995	**$3,877,083,108**
Average, 2013–2020	$2,057,714,138	--	$1,573,078,749	**$484,635,389**

* Discounted at a 3% rate to show present value

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

B vitamins and CHD Analysis

Figure 8.5—B Vitamins and Coronary Heart Disease Cost Analysis for All U.S. Adults over the Age of 55, 2013–2020

Year	Number of adults over the age of 55 with CHD (people)	Expected number of adults over the age of 55 with CHD who will experience a new CHD-related hospitalization event (people)	Mean CHD expenditure per person experiencing a CHD event ($)	Total CHD event expenditure among all U.S. adults over the age of 55* ($)	Total CHD event expenditure among all U.S. adults over the age of 55 given B vitamin intervention at preventive daily intake levels* ($)	Change in CHD event expenditure among all U.S. adults over the age of 55 given B vitamin intervention at preventive daily intake levels (avoided costs = benefits)* ($)
2013	17,256,590	4,899,840	$13,982.49	$68,511,963,964	$67,179,727,997	**$1,332,235,968**
2014	17,515,439	4,973,338	$14,681.61	$70,889,927,762	$69,511,451,565	**$1,378,476,197**
2015	17,789,118	5,051,046	$15,415.69	$73,395,594,202	$71,968,394,559	**$1,427,199,643**
2016	18,089,309	5,136,283	$16,186.48	$76,083,351,550	$74,603,887,649	**$1,479,463,901**
2017	18,405,872	5,226,168	$16,995.80	$78,918,010,400	$77,383,425,696	**$1,534,584,704**
2018	18,739,479	5,320,892	$17,845.59	$81,908,562,433	$80,315,825,535	**$1,592,736,898**
2019	19,102,556	5,423,984	$18,737.87	$85,116,813,467	$83,461,691,153	**$1,655,122,315**
2020	19,484,607	5,532,464	$19,674.77	$88,504,958,469	$86,783,952,645	**$1,721,005,824**
Cumulative, 2013–2020	--	--	--	$623,329,182,248	$611,208,356,798	**$12,120,825,450**
Average, 2013–2020	18,297,871	5,195,502	$16,690	$77,916,147,781	$76,401,044,600	**$1,515,103,181**

* Discounted at a 3% rate to show present value

Source: Summary Health Statistics for U.S. Adults: National Health Interview Survey 2011, Centers for Disease Control and Prevention and Frost & Sullivan

Figure 8.6—B Vitamins and Coronary Heart Disease, Number of Avoided CHD Events Given Use of B Vitamins for All U.S. Adults over the Age of 55, 2013–2020

Year	Number of avoided events (events)
2013	95,279
2014	96,708
2015	98,219
2016	99,877
2017	101,624
2018	103,466
2019	105,471
2020	107,580
Cumulative, 2013–2020	**808,225**
Average, 2013–2020	**101,028**

Source: Summary Health Statistics for U.S. Adults: National Health Interview Survey 2011, Centers for Disease Control and Prevention and Frost & Sullivan

Figure 8.7—B Vitamins Retail Prices of Best-selling Brands, 2013

Best-selling brand	Price per daily dose ($)	Annual cost of supplement utilization per person ($)
Source Naturals, Homocysteine Defense, 120 Tablets	$0.17	$61.30
Nutricology, Homocysteine, 90 Veggie Caps	$0.14	$50.45
Superior Source - Vitamin B12 1,000 mcg with Vitamin B6 2 mg & Folic Acid 400 mcg Microlingual	$0.17	$60.81
Carlson Laboratories - Tri-B	$0.07	$24.32
The Vitamin Shoppe - Homocysteine Blocker	$0.07	$26.46
Solgar - Homocysteine Modulators	$0.16	$58.32
Country Life - Homocysteine Shield	$0.22	$79.08
KAL - B6 B12 Folic Acid Lozenge Berry	$0.12	$44.38
Source Naturals - Homocysteine Defense	$0.13	$46.54
Source Naturals Homocysteine Defense™	$0.33	$119.32
Mason Natural Folic Acid B6 & B12 Tablets	$0.04	$15.38
Median price	$0.14	$50.45

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

Figure 8.8—B Vitamins and Coronary Heart Disease Cost Analysis for All U.S. Adults over the Age of 55, 2013–2020

Year	Change in CHD event expenditure among all U.S. adults over the age of 55 given B vitamin intervention at preventive daily intake levels (avoided costs = benefits)* ($)	Expected per person cost of B vitamin at preventive annual intake levels ($)	Expected cost of B vitamin supplementation of people with CHD at preventive daily intake levels among all U.S. adults over the age of 55* (supplement utilization costs) ($)	Net cost savings derived from avoided CHD events given required B vitamin supplement expenditures among all U.S. adults over the age of 55, 2013–2020 ($)
2013	$1,332,235,968	$50.45	$870,510,134	**$461,725,834**
2014	$1,378,476,197	$46.98	$866,411,130	**$512,065,067**
2015	$1,427,199,643	$47.45	$862,862,419	**$564,337,223**
2016	$1,479,463,901	$47.93	$860,385,879	**$619,078,023**
2017	$1,534,584,704	$48.40	$858,443,745	**$676,140,959**
2018	$1,592,736,898	$48.89	$857,032,106	**$735,704,792**
2019	$1,655,122,315	$49.38	$856,673,275	**$798,449,039**
2020	$1,721,005,824	$49.87	$856,839,620	**$864,166,205**
Cumulative, 2013–2020	$12,120,825,450	--	$6,889,158,308	**$5,231,667,142**
Average, 2013–2020	$1,515,103,181	--	$861,144,789	**$653,958,393**

* Discounted at a 3% rate to show present value

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

Phytosterols and CHD Analysis

Figure 8.9—Phytosterols and Coronary Heart Disease Cost Analysis for All U.S. Adults over the Age of 55, 2013–2020

Year	Number of adults over the age of 55 with CHD (people)	Expected number of adults over the age of 55 with CHD who will experience a new CHD-related hospitalization event (people)	Mean CHD expenditure per person experiencing a CHD event ($)	Total CHD event expenditure among all U.S. adults over the age of 55* ($)	Total CHD event expenditure among all U.S. adults over the age of 55 given phytosterol intervention at preventive daily intake levels* ($)	Change in CHD event expenditure among all U.S. adults over the age of 55 given phytosterol intervention at preventive daily intake levels (avoided costs = benefits)* ($)
2013	17,256,590	4,899,840	$13,982.49	$68,511,963,964	$64,774,976,543	**$3,736,987,421**
2014	17,515,439	4,973,338	$14,681.61	$70,889,927,762	$67,023,234,224	**$3,866,693,538**
2015	17,789,118	5,051,046	$15,415.69	$73,395,594,202	$69,392,229,002	**$4,003,365,200**
2016	18,089,309	5,136,283	$16,186.48	$76,083,351,550	$71,933,382,534	**$4,149,969,016**
2017	18,405,872	5,226,168	$16,995.80	$78,918,010,400	$74,613,424,820	**$4,304,585,580**
2018	18,739,479	5,320,892	$17,845.59	$81,908,562,433	$77,440,857,089	**$4,467,705,343**
2019	19,102,556	5,423,984	$18,737.87	$85,116,813,467	$80,474,113,961	**$4,642,699,506**
2020	19,484,607	5,532,464	$19,674.77	$88,504,958,469	$83,677,452,478	**$4,827,505,991**
Cumulative, 2013–2020	--	--	--	$623,329,182,248	$589,329,670,652	**$33,999,511,596**
Average, 2013–2020	18,297,871	5,195,502	$16,690	$77,916,147,781	$73,666,208,832	**$4,249,938,949**

* Discounted at a 3% rate to show present value

Source: Summary Health Statistics for U.S. Adults: National Health Interview Survey 2011, Centers for Disease Control and Prevention and Frost & Sullivan

Figure 8.10—Phytosterols and Coronary Heart Disease, Number of Avoided CHD Events Given Use of Phytosterols for All U.S. Adults over the Age of 55, 2013–2020

Year	Number of avoided events (events)
2013	267,262
2014	271,271
2015	275,509
2016	280,159
2017	285,061
2018	290,228
2019	295,851
2020	301,768
Cumulative, 2013–2020	**2,267,111**
Average, 2013–2020	**283,389**

Source: Summary Health Statistics for U.S. Adults: National Health Interview Survey 2011, Centers for Disease Control and Prevention and Frost & Sullivan

Figure 8.11—Phytosterol Retail Prices of Best-selling Brands, 2013

Best-selling brand		Price per daily dose ($)	Annual cost of supplement utilization per person ($)
Source Naturals Mega Strength Beta Sitosterol		$0.20	$74.6
Source Naturals, Phytosterol Complex, with Beta-Sitosterol, 113 mg, 180 Tablets		$0.15	$54.5
Phytosterol Complex 1000 mg (Per Serving)		$0.14	$51.1
Phytosterol Complex (650 MG) (60 Tablets , $0.20/serving)		$0.20	$73.0
Vitacost Phytosterol Complex with Beta-sitosterol -- 240 Tablets		$0.08	$28.4
Phytosterol Complex 1000mg w/ Beta Sitosterol, 100 Softgels		$0.12	$43.8
Nature Made CholestOff Complete Dietary Supplement Softgels		$0.70	$255.6
	Median Price	$0.15	$54.48

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

Figure 8.12—Phytosterols and Coronary Heart Disease Cost Analysis for All U.S. Adults over the Age of 55, 2013–2020

Year	Change in CHD event expenditure among all U.S. adults over the age of 55 given phytosterol intervention at preventive daily intake levels (avoided costs = benefits)* ($)	Expected per person cost of phytosterol at preventive annual intake levels ($)	Expected cost of phytosterol supplementation of people with CHD at preventive daily intake levels among all U.S. adults over the age of 55* (supplement utilization costs) ($)	Net cost savings derived from avoided CHD events given required phytosterol supplement expenditures among all U.S. adults over the age of 55, 2013–2020 ($)
2013	$3,736,987,421	$54.48	$882,156,894	**$2,796,794,456**
2014	$3,866,693,538	$51.63	$877,982,643	**$2,930,927,695**
2015	$4,003,365,200	$52.15	$874,448,578	**$3,071,432,136**
2016	$4,149,969,016	$52.67	$871,913,952	**$3,220,710,736**
2017	$4,304,585,580	$53.20	$869,999,763	**$3,377,424,898**
2018	$4,467,705,343	$53.73	$868,536,790	**$3,542,069,300**
2019	$4,642,699,506	$54.27	$868,216,338	**$3,717,451,017**
2020	$4,827,505,991	$54.81	$868,342,148	**$3,902,077,842**
Cumulative, 2013–2020	$33,999,511,596	--	$6,981,597,105	**$26,558,888,081**
Average, 2013–2020	$4,249,938,949	--	$872,699,638	**$3,319,861,010**

* Discounted at a 3% rate to show present value

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

Psyllium Dietary Fiber and CHD Analysis

Figure 8.13—Psyllium Dietary Fiber and Coronary Heart Disease Cost Analysis for All U.S. Adults over the Age of 55, 2013–2020

Year	Number of adults over the age of 55 with CHD (people)	Expected number of adults over the age of 55 with CHD who will experience a new CHD-related hospitalization event (people)	Mean CHD expenditure per person experiencing a CHD event ($)	Total CHD event expenditure among all U.S. adults over the age of 55* ($)	Total CHD event expenditure among all U.S. adults over the age of 55 given psyllium dietary fiber intervention at preventive daily intake levels* ($)	Change in CHD event expenditure among all U.S. adults over the age of 55 given psyllium dietary fiber intervention at preventive daily intake levels (avoided costs = benefits)* ($)
2013	17,256,590	4,899,840	$13,982.49	$68,511,963,964	$64,659,250,924	**$3,852,713,041**
2014	17,515,439	4,973,338	$14,681.61	$70,889,927,762	$66,903,491,914	**$3,986,435,848**
2015	17,789,118	5,051,046	$15,415.69	$73,395,594,202	$69,268,254,295	**$4,127,339,906**
2016	18,089,309	5,136,283	$16,186.48	$76,083,351,550	$71,804,867,855	**$4,278,483,695**
2017	18,405,872	5,226,168	$16,995.80	$78,918,010,400	$74,480,122,034	**$4,437,888,366**
2018	18,739,479	5,320,892	$17,845.59	$81,908,562,433	$77,302,502,872	**$4,606,059,561**
2019	19,102,556	5,423,984	$18,737.87	$85,116,813,467	$80,330,340,591	**$4,786,472,877**
2020	19,484,607	5,532,464	$19,674.77	$88,504,958,469	$83,527,956,090	**$4,977,002,379**
Cumulative, 2013–2020	--	--	--	$623,329,182,248	$588,276,786,575	**$35,052,395,672**
Average, 2013–2020	18,297,871	5,195,502	$16,690	$77,916,147,781	$73,534,598,322	**$4,381,549,459**

* Discounted at a 3% rate to show present value

Source: Summary Health Statistics for U.S. Adults: National Health Interview Survey 2011, Centers for Disease Control and Prevention and Frost & Sullivan

Figure 8.14—Psyllium Dietary Fiber and Coronary Heart Disease, Number of Avoided CHD Events Given Use of Dietary fibers for All U.S. Adults over the Age of 55, 2013–2020

Year	Number of avoided events (events)
2013	275,538
2014	279,671
2015	284,041
2016	288,835
2017	293,889
2018	299,216
2019	305,013
2020	311,113
Cumulative, 2013–2020	**2,337,318**
Average, 2013–2020	**292,165**

Source: Summary Health Statistics for U.S. Adults: National Health Interview Survey 2011, Centers for Disease Control and Prevention and Frost & Sullivan

Figure 8.15—Psyllium Dietary Fiber Retail Prices of Best-selling Brands, 2013

Best-selling brand	Price per daily dose ($) (at 10 grams per day)	Annual cost of supplement utilization per person ($)
Health Plus Inc. THE ORIGINAL Colon Cleanse®	$0.19	$68.41
Psyllium Husk Seed 100% Natural	$0.44	$159.66
Organic India USA - Psyllium Organic Whole Husk	$0.36	$133.05
Yerba Prima Psyllium Husks Powder -- 12 oz	$0.21	$78.07
100% Natural Psyllium Husk Seed, 8 oz. Powder	$0.15	$53.19
Metamucil Fiber Supplement Smooth Texture, Orange, 114 doses	$0.47	$171.67
Now Foods, Psyllium Husk Fiber, Orange-Flavored, 12 oz (340 g)	$0.33	$119.53
Source Naturals Psyllium Husk Powder -- 12 oz	$0.18	$64.19
Psyllium Whole Husk	$0.33	$119.71
Equate Fiber Original Texture (NBE) to Metamucil Fiber Powder	$0.28	$103.08
Median price	$0.30	$111.31

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

Figure 8.16—Psyllium Dietary Fiber and Coronary Heart Disease Cost Analysis for All U.S. Adults over the Age of 55, 2013–2020

Year	Change in CHD event expenditure among all U.S. adults over the age of 55 given psyllium dietary fiber intervention at preventive daily intake levels (avoided costs = benefits)* ($)	Expected per person cost of psyllium dietary fiber at preventive annual intake levels ($)	Expected cost of psyllium dietary fiber supplementation of people with CHD at preventive daily intake levels among all U.S. adults over the age of 55* (supplement utilization costs) ($)	Net cost savings derived from avoided CHD events given required psyllium dietary fiber supplement expenditures among all U.S. adults over the age of 55, 2013–2020 ($)
2013	$3,852,713,041	$111.31	$1,920,822,260	$1,931,890,781
2014	$3,986,435,848	$112.42	$1,911,777,611	$2,074,658,236
2015	$4,127,339,906	$113.55	$1,903,947,212	$2,223,392,695
2016	$4,278,483,695	$114.68	$1,898,482,606	$2,380,001,089
2017	$4,437,888,366	$115.83	$1,894,197,196	$2,543,691,170
2018	$4,606,059,561	$116.99	$1,891,082,345	$2,714,977,216
2019	$4,786,472,877	$118.16	$1,890,290,569	$2,896,182,308
2020	$4,977,002,379	$119.34	$1,890,657,616	$3,086,344,764
Cumulative, 2013–2020	$35,052,395,672	--	$15,201,257,415	$19,851,138,258
Average, 2013–2020	$4,381,549,459	--	$1,900,157,177	$2,481,392,282

* Discounted at a 3% rate to show present value

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

Chromium Picolinate and Diabetes Analysis

Figure 8.17—Chromium Picolinate and Diabetes Cost Analysis for All Diabetic Adults over the Age of 55 Diagnosed with CHD, 2013–2020

Year	Number of diabetic adults over the age of 55 diagnosed with CHD (people)	Expected number of diabetic people with CHD who will experience a new CHD-related hospitalization event (people)	Mean CHD expenditure per person experiencing a CHD event ($)	Total CHD event expenditure among all diabetics over the age of 55* ($)	Total CHD event expenditure among all diabetics over the age of 55 given chromium picolinate intervention at preventive daily intake levels* ($)	Change in CHD event expenditure among all diabetics over the age of 55 given chromium picolinate intervention at preventive daily intake levels (avoided costs = benefits)* ($)
2013	7,254,786	2,059,926	$13,982.49	$28,802,888,195	$27,731,554,231	$1,071,333,964
2014	7,363,608	2,090,825	$14,681.61	$29,802,600,091	$28,694,081,478	$1,108,518,614
2015	7,478,664	2,123,494	$15,415.69	$30,855,999,033	$29,708,298,860	$1,147,700,173
2016	7,604,867	2,159,328	$16,186.48	$31,985,950,211	$30,796,221,091	$1,189,729,120
2017	7,737,952	2,197,116	$16,995.80	$33,177,659,764	$31,943,604,571	$1,234,055,193
2018	7,878,202	2,236,939	$17,845.59	$34,434,907,854	$33,154,088,858	$1,280,818,995
2019	8,030,842	2,280,279	$18,737.87	$35,783,678,061	$34,452,691,064	$1,330,986,997
2020	8,191,459	2,325,885	$19,674.77	$37,208,076,896	$35,824,108,864	$1,383,968,033
Cumulative, 2013–2020	--	--	--	$262,051,760,105	$252,304,649,017	$9,747,111,087
Average, 2013–2020	7,692,548	2,184,224	$16,690.00	$32,756,470,013	$31,538,081,127	$1,218,388,886

* Discounted at a 3% rate to show present value

Source: Summary Health Statistics for U.S. Adults: National Health Interview Survey 2011, Centers for Disease Control and Prevention and Frost & Sullivan

Figure 8.18—Chromium Picolinate and Diabetes, Number of Avoided Diabetes Events Given Use of Chromium Picolinate for All Diabetic Adults over the Age of 55 Diagnosed with CHD, 2013–2020

Year	Number of avoided events (events)
2013	76,620
2014	77,769
2015	78,984
2016	80,317
2017	81,723
2018	83,204
2019	84,816
2020	86,512
Cumulative, 2013–2020	649,944
Average, 2013–2020	81,243

Source: Summary Health Statistics for U.S. Adults: National Health Interview Survey 2011, Centers for Disease Control and Prevention and Frost & Sullivan

Figure 8.19—Chromium Picolinate Retail Prices of Best-selling Brands, 2013

Best-selling brand		Price per daily dose ($)	Annual cost of supplement utilization per person ($)
GNC Chromium Picolinate 200		$0.11	$40.5
Metagenics, Chromium Picolinate, 60 Tablets		$0.18	$65.4
Chromium Picolinate 500 mcg Yeast Free		$0.03	$10.9
Solgar - Chromium Picolinate		$0.09	$32.8
Vitacost Chromium Picolinate -- 500 mcg - 300 Capsules		$0.03	$12.2
Chromium Picolinate 500 mcg. Tablets, 250 Tablets		$0.08	$30.7
Nature's Bounty Ultra Chromium Picolinate 500 mcg Dietary Supplement Tablets		$0.10	$36.5
Finest Nutrition Chromium Picolinate 400 mcg Dietary Supplement Tablets		$0.10	$36.5
	Median Price	$0.09	$31.75

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

Figure 8.20–Chromium Picolinate and Diabetes Cost Analysis for All Diabetic Adults over the Age of 55 Diagnosed with CHD, 2013–2020

Year	Change in CHD event expenditure among all diabetics over the age of 55 given chromium picolinate intervention at preventive daily intake levels (avoided costs = benefits)* ($)	Expected per person cost of chromium picolinate at preventive annual intake levels ($)	Expected cost of chromium picolinate supplementation at preventive daily intake levels among diabetics over the age of 55* (supplement utilization costs) ($)	Net cost savings derived from avoided CHD events given required chromium picolinate supplement utilization among diabetics over the age of 55 ($)
2013	$1,071,333,964	$34.67	$251,489,108	**$819,844,856**
2014	$1,108,518,614	$35.01	$250,304,912	**$858,213,702**
2015	$1,147,700,173	$35.36	$249,279,694	**$898,420,478**
2016	$1,189,729,120	$35.72	$248,564,225	**$941,164,895**
2017	$1,234,055,193	$36.07	$248,003,146	**$986,052,047**
2018	$1,280,818,995	$36.43	$247,595,325	**$1,033,223,670**
2019	$1,330,986,997	$36.80	$247,491,660	**$1,083,495,337**
2020	$1,383,968,033	$37.17	$247,539,716	**$1,136,428,316**
Cumulative, 2013–2020	$9,747,111,087	--	$1,990,267,786	**$7,756,843,301**
Average, 2013–2020	$1,218,388,886	--	$248,783,473	**$969,605,413**

* Discounted at a 3% rate to show present value

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

Lutein and Zeaxanthin and ARED Analysis

Figure 8.21—Lutein and Zeaxanthin and Age-related Eye Disease Cost Analysis for All U.S. Adults over the Age of 55, 2013–2020

Year	Number of people with age-related macular degeneration (people)	Expected number of people with age-related macular degeneration that will experience a new event (people)	Number of people with cataracts (people)	Expected number of people with cataracts that will experience a new cataracts-related event (people)	Mean age-related eye disease expenditure per person ($)
2013	2,155,514	1,077,757	25,391,784	3,790,874	$3,712
2014	2,187,846	1,093,923	25,772,660	3,847,737	$3,898
2015	2,222,031	1,111,016	26,175,358	3,907,858	$4,093
2016	2,259,528	1,129,764	26,617,067	3,973,803	$4,297
2017	2,299,070	1,149,535	27,082,866	4,043,345	$4,512
2018	2,340,741	1,170,370	27,573,743	4,116,631	$4,738
2019	2,386,092	1,193,046	28,107,984	4,196,390	$4,975
2020	2,433,814	1,216,907	28,670,144	4,280,318	$5,223
Cumulative, 2013–2020	--	--	--	--	--
Average, 2013–2020	2,285,580	1,142,790	26,923,951	4,019,620	**$4,431**

* Discounted at a 3% rate to show present value

Source: Summary Health Statistics for U.S. Adults: National Health Interview Survey 2011, Centers for Disease Control and Prevention and Frost & Sullivan

Figure 8.22—Lutein and Zeaxanthin and Age-related Eye Disease Cost Analysis for All U.S. Adults over the Age of 55, 2013–2020 (continued)

Year	Total age-related macular degeneration event expenditure among all U.S. adults over the age of 55* ($)	Total age-related macular degeneration event expenditure given lutein and zeaxanthin supplement intervention at preventive daily intake levels among all U.S. adults over the age of 55* ($)	Change in age-related macular degeneration event expenditure given lutein and zeaxanthin supplement intervention at preventive daily intake levels among all U.S. adults over the age of 55 (avoided costs = benefits)* ($)	Total cataracts event expenditure among all U.S. adults over the age of 55* ($)	Total cataract event expenditure given lutein and zeaxanthin supplement intervention at preventive daily intake levels among all U.S. adults over the age of 55* ($)	Change in cataract event expenditure given lutein and zeaxanthin supplement intervention at preventive daily intake levels among all U.S. adults over the age of 55 (avoided costs = benefits)* ($)
2013	$4,000,760,135	$3,950,326,584	**$50,433,551**	$14,072,171,747	$10,720,724,847	**$3,351,446,900**
2014	$4,139,621,469	$4,087,437,434	**$52,184,036**	$14,560,599,068	$11,092,827,675	**$3,467,771,392**
2015	$4,285,940,007	$4,231,911,481	**$54,028,526**	$15,075,256,165	$11,484,913,362	**$3,590,342,802**
2016	$4,442,891,755	$4,386,884,696	**$56,007,058**	$15,627,314,241	$11,905,492,562	**$3,721,821,679**
2017	$4,608,421,824	$4,550,328,094	**$58,093,729**	$16,209,545,487	$12,349,058,851	**$3,860,486,637**
2018	$4,783,055,284	$4,722,760,127	**$60,295,157**	$16,823,796,771	$12,817,019,242	**$4,006,777,529**
2019	$4,970,401,290	$4,907,744,451	**$62,656,839**	$17,482,762,840	$13,319,045,087	**$4,163,717,753**
2020	$5,168,252,216	$5,103,101,269	**$65,150,947**	$18,178,678,643	$13,849,220,668	**$4,329,457,974**
Cumulative, 2013–2020	$36,399,343,979	$35,940,494,136	**$458,849,843**	$128,030,124,962	$97,538,302,295	**$30,491,822,667**
Average, 2013–2020	$4,549,917,997	$4,492,561,767	**$57,356,230**	$16,003,765,620	$12,192,287,787	**$3,811,477,833**

* Discounted at a 3% rate to show present value

Source: Summary Health Statistics for U.S. Adults: National Health Interview Survey 2011, Centers for Disease Control and Prevention and Frost & Sullivan

Figure 8.23—Lutein and Zeaxanthin and Age-related Eye Disease, Number of Avoided Age-related Eye Disease Events Given Use of Lutein and Zeaxanthin for All U.S. Adults over the Age of 55, 2013–2020

Year	Number of avoided age-related macular disease events	Number of avoided cataract events
2013	13,586	902,840
2014	13,790	916,382
2015	14,005	930,701
2016	14,242	946,406
2017	14,491	962,968
2018	14,754	980,422
2019	15,040	999,418
2020	15,340	1,019,406
Cumulative, 2013–2020	**115,248**	**7,658,543**
Average, 2013–2020	**14,406**	**957,318**

Source: Summary Health Statistics for U.S. Adults: National Health Interview Survey 2011, Centers for Disease Control and Prevention and Frost & Sullivan

Figure 8.24—Lutein and Zeaxanthin Retail Prices of Best-selling Brands, 2013

Best-selling brands		Price per daily dose ($)	Annual cost of supplement utilization per person ($)
Nature Made Lutein 20 mg Dietary Supplement Liquid Softgels		$0.57	$206.85
Source Naturals® Zeaxanthin With Lutein		$0.38	$136.97
Jarrow Formulas, Lutein, 20 mg, 60 Softgels		$0.19	$71.04
Source Naturals, Lutein, 20 mg, 60 Capsules		$0.30	$110.79
Puritan's Pride Lutein 20 mg		$0.11	$38.78
Jarrow's Formula - Lutein + ZEAXANTHIN		$0.28	$102.21
	Median Price	$0.29	$106.50

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

Figure 8.25—Lutein and Zeaxanthin and Age-related Eye Disease Cost Analysis for All U.S. Adults over the Age of 55, 2013–2020

Year	Total change in ARED event expenditure given lutein and zeaxanthin supplement intervention at preventive daily intake levels among all U.S. adults over the age of 55 (avoided costs = benefits)* ($)	Expected per person cost of lutein and zeaxanthin at preventive annual intake levels ($)	Expected cost of lutein and zeaxanthin supplementation among people with age-related eye disease at preventive daily intake levels among all U.S. adults over the age of 55* (supplement utilization costs) ($)	Net total cost savings derived from avoided ARED events given required lutein and zeaxanthin supplement expenditures ($)
2013	$3,401,880,451	$106.50	$2,933,809,533	**$468,070,918**
2014	$3,519,955,428	$107.57	$2,919,994,993	**$599,960,435**
2015	$3,644,371,328	$108.64	$2,908,035,062	**$736,336,266**
2016	$3,777,828,737	$109.73	$2,899,688,578	$878,140,159
2017	$3,918,580,366	$110.83	$2,893,143,164	$1,025,437,202
2018	$4,067,072,686	$111.93	$2,888,385,629	$1,178,687,057
2019	$4,226,374,593	$113.05	$2,887,176,293	$1,339,198,300
2020	$4,394,608,921	$114.18	$2,887,736,910	$1,506,872,011
Cumulative, 2013–2020	$30,950,672,510	--	$23,217,970,163	$7,732,702,347
Average, 2013–2020	$3,868,834,064	--	$2,902,246,270	$966,587,794

* Discounted at a 3% rate to show present value

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

Calcium and Vitamin D and Osteoporosis Analysis

Figure 8.26—Calcium and Vitamin D and Osteoporosis Cost Analysis for All U.S. Women over the Age of 55, 2013–2020

Year	Number of women over the age of 55 with osteoporosis (people)	Expected number of women with osteoporosis that will experience a new osteoporosis-attributed fracture (people)	Mean osteoporosis expenditure per person experiencing a osteoporosis-attributed fracture ($)	Total expenditure on osteoporosis-attributed fracture treatment for all U.S. women over the age of 55* ($)	Total osteoporosis-attributed fracture expenditure given calcium and vitamin D supplement intervention at preventive daily intake levels among all U.S. women over the age of 55* ($)	Change in expenditure on osteoporosis-attributed fracture treatment for all U.S. women over the age of 55 given calcium and vitamin D supplement intervention at preventive daily intake levels (avoided costs = benefits)* ($)
2013	8,322,446	1,289,979	$11,571.62	$14,927,148,160	$13,278,693,236	$1,648,454,924
2014	8,447,283	1,309,329	$12,150.20	$15,445,250,633	$13,739,579,918	$1,705,670,714
2015	8,579,272	1,329,787	$12,757.71	$15,991,176,512	$14,225,217,376	$1,765,959,136
2016	8,724,047	1,352,227	$13,395.60	$16,576,775,725	$14,746,146,908	$1,830,628,817
2017	8,876,718	1,375,891	$14,065.38	$17,194,381,325	$15,295,548,255	$1,898,833,070
2018	9,037,608	1,400,829	$14,768.64	$17,845,952,389	$15,875,164,146	$1,970,788,243
2019	9,212,712	1,427,970	$15,507.08	$18,544,954,954	$16,496,973,519	$2,047,981,436
2020	9,396,966	1,456,530	$16,282.43	$19,283,152,190	$17,153,649,163	$2,129,503,027
Cumulative, 2013–2020	--	--	--	$135,808,791,888	$120,810,972,521	$14,997,819,367
Average, 2013–2020	8,824,632	1,367,818	$13,812.00	$16,976,098,986	$15,101,371,565	$1,874,727,421

* Discounted at a 3% rate to show present value

Source: Summary Health Statistics for U.S. Adults: National Health Interview Survey 2011, Centers for Disease Control and Prevention and Frost & Sullivan

Figure 8.27—Calcium and Vitamin D and Osteoporosis, Number of Avoided Osteoporosis Events Given Use of Calcium and Vitamin D for All U.S. Women over the Age of 55, 2013–2020

Year	Number of avoided osteoporosis-attributed fractures (events)
2013	142,457
2014	144,594
2015	146,853
2016	149,331
2017	151,944
2018	154,698
2019	157,696
2020	160,849
Cumulative, 2013–2020	1,208,422
Average, 2013–2020	151,053

Source: Summary Health Statistics for U.S. Adults: National Health Interview Survey 2011, Centers for Disease Control and Prevention and Frost & Sullivan

Figure 8.28—Calcium and Vitamin D Retail Prices of Best-selling Brands, 2013

Best-selling brand	Price per daily dose ($)	Annual cost of supplement utilization per person ($)
GNC Calcium 600 with Vitamin D-3	$0.06	$21.3
Twinlab, Calcium 1000 Tabs, with Vitamin D3, 120 Tablets	$0.12	$43.2
Puritan's Pride - Calcium 600 + Vitamin D3, 250 Servings	$0.07	$26.3
Puritan's Pride - Calcium 600 + Vitamin D3, 500 Servings	$0.07	$24.8
Calcium Citrate + Vitamin D	$0.28	$103.4
Schiff Super Calcium Magnesium With Vitamin D	$0.20	$72.9
Calcium 600 mg + Vitamin D3, 500 Caplet	$0.07	$24.1
Nature Made Calcium 600 mg with Vitamin D Dietary Supplement Liquid Softgels	$0.32	$116.8
Nature's Bounty Coral Calcium 1000 mg Plus Vitamin D & Magnesium Capsules	$0.23	$85.2
Median Price	$0.16	$57.55

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

Figure 8.29—Calcium and Vitamin D and Osteoporosis Cost Analysis for All U.S. Women over the Age of 55, 2013–2020

Year	Change in expenditure on osteoporosis-attributed fracture treatment for all U.S. women over the age of 55 given calcium and vitamin D supplement intervention at preventive daily intake levels (avoided costs = benefits)* ($)	Expected per person cost of calcium and vitamin D at preventive annual intake levels ($)	Expected cost of calcium and vitamin D among people with osteoporosis at preventive daily intake levels among all U.S. women over the age of 55* (supplement utilization costs) ($)	Net cost savings derived from avoided osteoporosis-attributed fractures given required calcium and vitamin D dietary supplement expenditures among all U.S. women over the age of 55, 2013–2020
2013	$1,648,454,924	$43.22	$359,706,531	$1,288,748,393
2014	$1,705,670,714	$43.65	$358,012,768	$1,347,657,947
2015	$1,765,959,136	$44.09	$356,546,392	$1,409,412,744
2016	$1,830,628,817	$44.53	$355,523,052	$1,475,105,764
2017	$1,898,833,070	$44.98	$354,720,537	$1,544,112,533
2018	$1,970,788,243	$45.43	$354,137,228	$1,616,651,015
2019	$2,047,981,436	$45.88	$353,988,955	$1,693,992,481
2020	$2,129,503,027	$46.34	$354,057,690	$1,775,445,336
Cumulative, 2013–2020	$14,997,819,367	--	$2,846,693,154	$12,151,126,213
Average, 2013–2020	$1,874,727,421	--	$355,836,644	$1,518,890,777

* Discounted at a 3% rate to show present value

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

Magnesium and Osteoporosis Analysis

Figure 8.30—Magnesium and Osteoporosis Cost Analysis for All U.S. Women over the Age of 55, 2013–2020

Year	Number of women over the age of 55 with osteoporosis (people)	Expected number of women with osteoporosis that will experience a new osteoporosis-attributed fracture (people)	Mean osteoporosis expenditure per person experiencing a osteoporosis-attributed fracture ($)	Total expenditure on osteoporosis-attributed fracture treatment for all U.S. women over the age of 55* ($)	Total osteoporosis-attributed fracture expenditure given magnesium supplement intervention at preventive daily intake levels among all U.S. women over the age of 55* ($)	Change in expenditure on osteoporosis-attributed fracture treatment for all U.S. women over the age of 55 given magnesium supplement intervention at preventive daily intake levels (avoided costs = benefits)* ($)
2013	8,322,446	1,289,979	$11,571.62	$14,927,148,160	$14,179,212,251	$747,935,909
2014	8,447,283	1,309,329	$12,150.20	$15,445,250,633	$14,671,354,812	$773,895,820
2015	8,579,272	1,329,787	$12,757.71	$15,991,176,512	$15,189,926,668	$801,249,844
2016	8,724,047	1,352,227	$13,395.60	$16,576,775,725	$15,746,183,994	$830,591,730
2017	8,876,718	1,375,891	$14,065.38	$17,194,381,325	$16,332,844,005	$861,537,320
2018	9,037,608	1,400,829	$14,768.64	$17,845,952,389	$16,951,767,614	$894,184,775
2019	9,212,712	1,427,970	$15,507.08	$18,544,954,954	$17,615,746,133	$929,208,821
2020	9,396,966	1,456,530	$16,282.43	$19,283,152,190	$18,316,955,445	$966,196,745
Cumulative, 2013–2020	--	--	--	$135,808,791,888	$129,003,990,923	$6,804,800,966
Average, 2013–2020	8,824,632	1,367,818	$13,812.00	$16,976,098,986	$16,125,498,865	$850,600,121

* Discounted at a 3% rate to show present value

Source: Summary Health Statistics for U.S. Adults: National Health Interview Survey 2011, Centers for Disease Control and Prevention and Frost & Sullivan

Figure 8.31—Magnesium and Osteoporosis, Number of Avoided Osteoporosis Events Given Use of Magnesium for All U.S. Women over the Age of 55, 2013–2020

Year	Number of avoided events (events)
2013	64,635
2014	65,605
2015	66,630
2016	67,754
2017	68,940
2018	70,190
2019	71,550
2020	72,981
Cumulative, 2013–2020	548,284
Average, 2013–2020	68,536

Source: Summary Health Statistics for U.S. Adults: National Health Interview Survey 2011, Centers for Disease Control and Prevention and Frost & Sullivan

Figure 8.32—Magnesium Retail Prices of Best-selling Brands, 2013

Best-selling brand	Price per daily dose ($)	Annual cost of supplement utilization per person ($)
GNC Super Magnesium	$0.33	$121.67
Solaray, Magnesium Asporotate, 120 Capsules	$0.18	$66.60
Solgar, Chelated Magnesium, 250 Tablets	$0.34	$122.42
Magnesium 250 mg	$0.02	$8.93
TwinLab Magnesium Caps	$0.04	$14.59
Vitacost Magnesium -- 400 mg - 200 Capsules	$0.03	$11.85
Nature Made Magnesium 250 mg Dietary Supplement Tablets	$0.08	$29.18
Nature's Bounty Magnesium 500 mg Dietary Supplement Tablets	$0.09	$32.84
Median Price	$0.09	$31.01

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

Figure 8.33—Magnesium and Osteoporosis Cost Analysis for All U.S. Women over the Age of 55, 2013–2020

Year	Change in expenditure on osteoporosis-attributed fracture treatment for all U.S. women over the age of 55 given magnesium intervention at preventive daily intake levels (avoided costs = benefits)* ($)	Expected per person cost of magnesium at preventive annual intake levels ($)	Expected cost of magnesium among people with osteoporosis at preventive daily intake levels among all U.S. women over the age of 55* (supplement utilization costs) ($)	Net cost savings derived from avoided osteoporosis-attributed fractures given required magnesium dietary supplement expenditures among all U.S. women over the age of 55, 2013–2020
2013	$747,935,909	$31.01	$258,076,771	$489,859,138
2014	$773,895,820	$31.32	$256,861,555	$517,034,266
2015	$801,249,844	$31.63	$255,809,482	$545,440,362
2016	$830,591,730	$31.95	$255,075,272	$575,516,459
2017	$861,537,320	$32.27	$254,499,495	$607,037,825
2018	$894,184,775	$32.59	$254,080,992	$640,103,784
2019	$929,208,821	$32.92	$253,974,611	$675,234,210
2020	$966,196,745	$33.25	$254,023,926	$712,172,819
Cumulative, 2013–2020	$6,804,800,966	--	$2,042,402,102	$4,762,398,863
Average, 2013–2020	$850,600,121	--	$255,300,263	$595,299,858

* Discounted at a 3% rate to show present value

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

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