Supplements to Savings

Health Care Cost Savings from the Targeted Use of Dietary Supplements 2022–2030

CRN FOUNDATION

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This report was funded through a grant from the CRN Foundation.

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7550 IH 10 West, Suite 400
San Antonio, TX 78229
Tel: +1.210.348.1000
myfrost@frost.com

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BACKGROUND

Problem Statement

According to the U.S. Centers for Disease Control (CDC), seventy five percent (75%) of the nation's health care spending was spent to cover the cost of chronic diseases affecting Americans, such as coronary artery disease, dementia, age-related eye disease, and osteoporosis. These diseases are potentially avoidable with some types of preventive care [1]. Preventable chronic diseases also reduce the total productivity of the U.S. workforce by more than $260 billion annually [1]. Yet, the U.S. only spends 2.9% of total health care expenditures on preventive care services annually according to the statistics collected by the Organization for Economic Co-operation and Development (OECD). This is comparable to other OECD countries but is only a fraction of what is needed [2].

Despite the U.S. health care system not having as strong an emphasis on preventive medicine as could be desired, the role of preventive care in maintaining individual and overall health and wellness as opposed to a continued reactive approach focused on single-event interventions is gaining more purchase. Most Americans are well aware of the issues facing the country's current health care system, including growing costs, denied tests and treatments, fragmented care, less time available for a patient-physician relationship, medical errors, and other inefficiencies. However, the last decade has shown that important cultural, technological, and demographic trends have increasingly put more control of their health into the hands of patients. This transformation has had an enormous impact on how medicine is practiced today (e.g., telemedicine) and how the health care system, as a whole, operates.

This shift has been driven by stakeholders looking for better ways to control escalating health care costs by identifying people at higher risk of disease early and working to minimize their chances of experiencing costly events, using more targeted or personalized solutions. One solution that is accessible to Americans today is the availability of certain dietary supplement products that have been scientifically shown to help reduce this risk. Dietary supplements, based on the Dietary Supplement Health and Education Act (DSHEA) of 1994, are defined as products that are orally ingested and contain nutrients or other dietary components meant to supplement the diet [3]. Dietary supplements come in many forms, including tablets, capsules, liquids, and powders and the active components of dietary supplements are often derived from nutrients found in food including vitamins, minerals, fiber and carbohydrates, fatty acids, proteins, and amino acids [3].

In the last several decades, and especially in the past decade, a significant amount of clinical research has been published exploring the association between the use of certain dietary supplements by certain subjects at high-risk of disease, particularly any effect on disease event

occurrence or event risk biomarkers. What is known is that many disease events require costly treatments, especially those associated with chronic diseases, and preventing at least some of these events from ever occurring would necessarily have an impact on future health care spending. In this update study, we examine the potential health care cost savings that could be realized if certain at-risk individuals were to use certain dietary supplements that have been shown to lower disease event risk. Specifically, this report will examine evidence that demonstrates that the use of key dietary supplement ingredients can reduce the direct and indirect medical costs associated with coronary artery disease (CAD), age-related cognitive decline disorders, age-related eye disease, diabetes, osteoporotic fractures, irritable bowel syndrome, and inadequate choline intake among expectant mothers in the United States.

Research Methodology

The overarching research methodology used in this economic report is based on a health-to-wealth Cost-Benefit Analysis (CBA) model created in 2013 to address this topic [4]. This model was built to allow the comparison of dietary supplement users versus non-users in terms of any changes in disease-attributed risk which in turn would imply that associated disease treatment and management costs were different as well. Specifically, this CBA can be used to assess various use (and non-use) scenarios and to identify the potential savings or loss that can be realized in one scenario versus another. The determination of whether a given dietary supplement regimen is cost-effective is based on the risk level faced by the user's risk profile, the supplement's effectiveness at reducing the risk of the potential supplement user and the magnitude of the economic consequences (costs) that could be incurred if the potential user did not use the supplement and experienced a medical event [4].

This issue is similar to the basic methodology of most clinical studies; the treatment's effect on the outcome of a given event can be assessed when a treatment regimen is applied to one group versus a control group. From these types of analyses, risk—and possible risk reduction—can be calculated using a cost-benefit model which can be useful to key decision makers (including patients, health care professionals, governments, insurance companies, and employers) in determining if a given regimen is cost-effective.

To find the true effect size of treatment with a given dietary supplement, a rigorous search for clinical research studies and meta-analyses of clinical research studies for each of the seven interventions was conducted to deduce the expected efficacy of dietary supplementation on the incidence of disease events that required medical treatment and/or resulted in increased costs due to disease management and productivity losses. The aim was to collect a comprehensive set of studies that represented the totality of evidence of efficacy for a given dietary supplement's effects on the relative risk of a specific disease event.

In summary, the process of deriving the risk reduction metric for each of the dietary supplements assessed followed the same general process: relevant and representative clinical studies and meta-analyses were identified through a rigorous search exercise that studied any effects on disease event occurrence and calculating an aggregated measure of relative risk between dietary supplement users versus non-users from the set of identified studies. Specifically, we undertook 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 of interest

We performed a rigorous scientific literature search to build a database of key studies (both clinical studies of various study protocol types and meta-analyses) that investigated the potential for a causal relationship between supplement intake and the incidence of specific health conditions of interest. Types of studies considered include randomized controlled trials, meta-analyses of randomized control trials, observational epidemiologic studies, and other types of clinical trials adhering to accepted scientific methodologies. 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 November 1, 2021, and April 15, 2022.

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 studies was created, each study's title, abstract, and, in some cases, full text was thoroughly assessed to determine whether the study directly tested for a quantifiable relationship between supplement use 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 if it directly tested a relationship between the intake of the dietary supplement of interest and a potential effect on the likelihood of a disease event occurring, independent of the direction of the relationship. Both primary and secondary outcomes were considered. Typically, it was observational epidemiologic studies and randomized clinical trials that fit this criterion. If such studies were not found, then studies were reviewed that tested for a potential causal relationship between supplement intake and the level of a biomarker that has been correlated with the relative risk of a disease event. The authors strove to include studies that were similar in methodology in a given meta-analysis in an attempt to control for observational variance. In addition, the research team strove for an ideal of exhaustive inclusion of all studies, although that cannot be guaranteed because of time and resource constraints. The authors make no claims of endorsing the specific findings of any scientific study reviewed, and any exclusion of relevant studies is accidental and should not be read as a judgment of any type.

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

The next step in the process was to conduct the actual meta-analysis, meaning that each qualified study's reported effect size was weighted by the reported precision of its findings and the size of its sample population in order to derive an overall expected risk reduction (RR) metric. A random-effects meta-analysis 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 [5]. This approach allowed us to properly combine the results of a number of studies that addressed the same research question, even though each study varied in terms of sample size, study protocol, research team, and a host of other qualities. The variance in study characteristics was addressed by controlling for inter-study and intra-study variance, which was expected to provide a more reliable estimate of the overall effect of the intervention [5]. Meta-analyses are increasingly common in the dietary supplement literature, and their - prevalence is a testament to the growth in research & development investment made by the dietary supplement industry to demonstrate the efficacy of its products. In cases where there was a recently published meta-analysis on the same topic, the authors defaulted to these findings because they were independently conducted and peer-reviewed, and it was assumed that their findings were objective.

Health Care Cost Savings Scenario Analysis

The key criterion for a given study's inclusion in the cost models was a measure of relative risk (RR) given use of the supplement of interest versus non-use of the supplement. RR can be used to derive the number needed to treat (NNT) given a certain baseline disease risk level [5]. The NNT is the total number of people within a target cohort who would have to adopt a specified dietary supplement regimen in order to realize one avoided undesired event. This criterion was selected as the variable of focus in the present study because it was easy to associate an expected health care cost with each person expected to experience an event. For example, if 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 was determined, the number of potentially avoided events if everybody in a given population were to use the supplement at the daily intake level found to be effective could be calculated. From the expected cost per event, the total avoided costs could also be estimated. For example, consider the case of magnesium. It has been found that 13.1 million people aged 55 and over had documented coronary artery disease (CAD) in 2021 and has been estimated that this target population will grow to 15.8 million people by 2030. If this target population had used magnesium at preventive daily intake levels, over 91,000 CAD events would have been avoided based on the supposition from current scientific literature that the expected

relative reduction of risk of experiencing a CAD event was 5.34%. This implies an NNT metric of 144 people who needed to be treated to avoid one such event. Given that the cost of each CAD event averaged $31,517 in 2021, the net potentially avoided direct and indirect medical costs would have been approximately $1.830 billion in 2021. Refer to Table 11 for a detailed description of the derivation of the relative risk metric for magnesium intake.

Once the expected effect size was determined from the literature, the potential cost savings derived from dietary supplement usage at preventive daily intake levels among a particular high-risk cohort was calculated and compared with zero usage [155]. The calculation of total cost savings is straightforward – the 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 cost of dietary supplement use by the entire target high-risk cohort EQUALS potential net cost savings [155].

Accordingly, if the potential net cost savings was positive, the dietary supplement regimen in question was considered an effective means of reducing overall disease-related individual lifetime costs and total social health care costs [155]. Of course, the prior cost-benefit analysis approach makes the assumption that in the supplementation scenario, the entire population of the target high-risk cohort used the given dietary supplements at protective intake levels, and this was compared to zero use in that population segment. In other words, the calculated net savings is actually the maximum potential net savings theoretically achievable. However, because it is likely that a percentage of the target high-risk cohort are already regular users of the dietary supplement in question at various intake levels, that share of the target population would have already reduced its risk of experiencing a disease event and would be already realizing its risk-reducing benefits, while the remainder of the potential regular users has yet to realize the potential preventive benefits from regular use of the given dietary supplements at protective intake levels. Because avoided expenditures and net cost savings are a 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 by the number of current users. 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 nutrient explored in this study was analyzed independently, and comparisons between them may be unwarranted. The definition of disease-attributed events and the associated per-person costs of treatment vary by disease condition, among other factors; thus, derived benefits and costs are not comparable across disease conditions. In addition, health benefits

of using different supplements, such as omega-3 fatty acids and magnesium in combination for reducing the risk of a single disease, such as CAD, may not be additive. This study does not control for average food intake of these ingredients because it is assumed that most of the clinical studies did not fully control for food intake either, suggesting that the observed effect sizes has taken into account some food-based intake. Finally, variability due to differences in sample size, research methodologies and study protocols, and patient population characteristics among the included studies was high, making comparison of the relative efficacy of dietary supplements unadvisable.

However, there is enough evidence to suggest that the net cost savings realizable if people were to use a combination of the studied dietary supplements is highly likely to be greater than that realized from using any single one. Certainly, more research is required to determine if cost savings from use of multiple supplements is additive (the sum of the savings from each supplement), synergistic (the savings from multiple supplements is higher than the sum of the savings from each supplement due to offsetting effects/differences in their mechanisms of action), or antagonistic (the net savings from using a combination of supplements is lower than the sum of the saving from each one). The authors do not endorse the specific findings of any scientific study reviewed.

Regarding cost estimate forecasts, expected compound annual growth rates (CAGR) were derived from a historic assessment of population growth rates and price inflation growth. Specifically, health care costs per person are expected to grow at an average annual growth rate of 2.2% from 2022 to 2030 based on the observed average price inflationary growth rate over the last 10 years. In 2022, price inflation is in fact much higher than it had been the last decade so it is likely that our projections will underestimate cost growth leading to conservative estimates. Given current inflation rates, we consider this expected growth rate to be conservative. Also, this growth rate was applied for all procedures for all conditions assessed in this study. Growth in the targeted population was expected to occur at the average annual growth rate of the population as a whole 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 were expected to grow at a compound annual growth rate of 2.2% per year, the same as price growth in general.

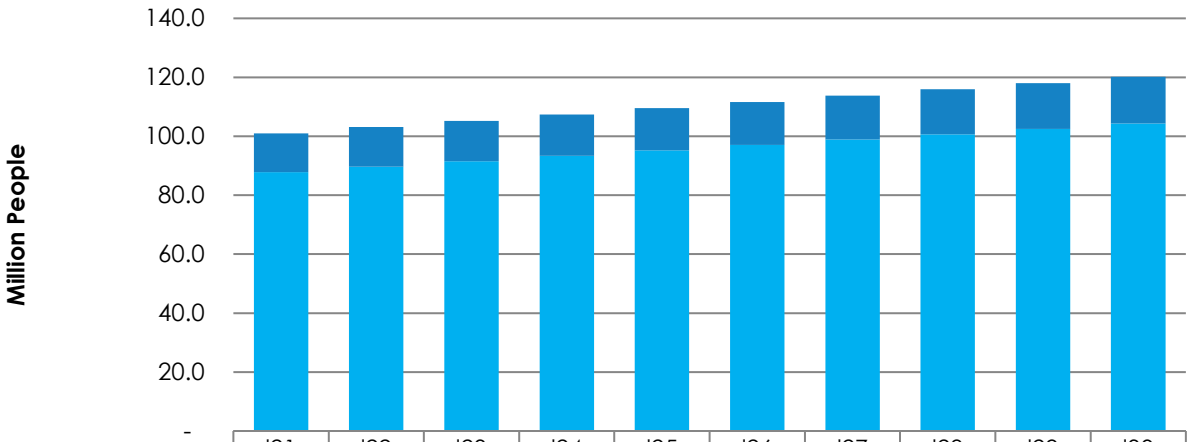
THE COST EFFECTIVENESS OF OMEGA-3, MAGNESIUM, SOLUBLE FIBER, AND VITAMIN K2 DIETARY SUPPLEMENTATION FOR MANAGING THE RISK OF CORONARY ARTERY DISEASE OUTCOMES

The Burden and Social Consequences

Coronary artery disease (CAD), also known as coronary heart disease (CHD) or ischemic heart disease (IHD), is caused by the buildup of plaque on arterial walls [6]. The plaque, being composed of cholesterol and other substances, causes the inside of arteries to narrow over time which in turn can cause blockages to occur and lead to heart attacks and heart failure.

CAD puts a heavy burden, both financially and in terms of reduced quality of life, on U.S. citizens, and Americans are increasingly struggling to cope with it, as well as the increasing costs of treating this disease condition. CAD continues to be the leading cause of death in the United States, ending 659,000 lives each year and accounting for 1 out of 4 deaths, according to the Centers for Disease Control and Prevention (CDC) [7]. According to the U.S. Department of Health & Human Services Agency for Healthcare Research and Quality, it is expected that 13.4 million U.S. adults aged 55 and older had experienced a CAD-attributed inpatient medical service or emergency room visit event in 2022, an event risk of 13.0% given a total population of 103.1 million Americans aged 55 and older [9].

Chart 1. Target Population Size of Coronary Artery Disease, United States, 2020-2030



	'21	'22	'23	'24	'25	'26	'27	'28	'29	'30
CAD Population	13.1	13.4	13.7	14.0	14.3	14.6	14.9	15.2	15.5	15.8
Heathy Adults	87.8	89.7	91.5	93.4	95.2	97.0	98.9	100.7	102.5	104.4
All Adults	101.0	103.1	105.2	107.4	109.5	111.7	113.8	115.9	118.1	120.2

Source: Agency for Healthcare Research and Quality. Medical Expenditure Panel Survey (MEPS)., US Census, and Frost & Sullivan analysis

Table 1. Target Population Size of Coronary Artery Disease, United States, 2020-2030

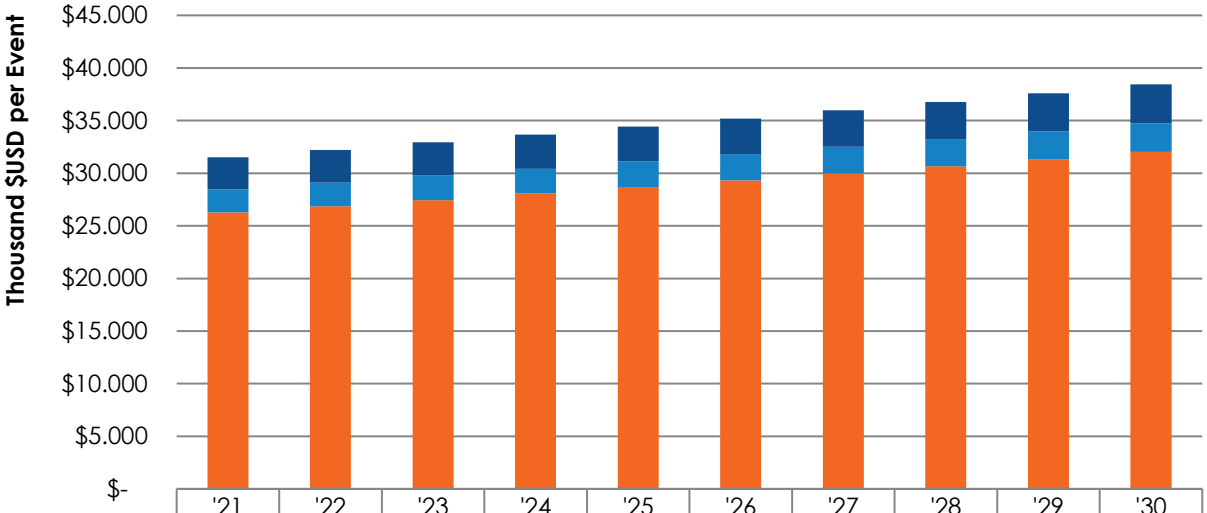
Year	Total Population, age 55 and older (million people)	Population of people experiencing CAD-attributed inpatient medical service or emergency room visits event, age 55 and older (million people)
2021	100.97	13.12
2022	103.11	13.43
2023	105.25	13.73
2024	107.38	14.03
2025	109.52	14.33
2026	111.66	14.63
2027	113.80	14.93
2028	115.93	15.23
2029	118.07	15.54
2030	120.21	15.84
Average ('22-'30)	111.66	14.63
CAGR	2.0%	2.0%

Source: Agency for Healthcare Research and Quality. Medical Expenditure Panel Survey (MEPS)., US Census, and Frost & Sullivan analysis

Though the degree of effect varies, every CAD-attributed medical event entails financial burdens, including direct medical costs such as the costs of emergency room visits, hospitalization, surgery, medication, rehabilitation, and other costs tied to treating a medical event as well as indirect costs related to post-event disease management and the consequences of disability (e.g., lost wages and productivity losses). Based on a review of the Medical Expenditure Panel Survey (MEPS) database and Frost & Sullivan's analysis, the total expected direct medical expenditures on all CAD-attributed medical events for all U.S. adults aged 55 exceeded $413.6 billion in 2021 [9]. This is based on a mean per person expenditure on CAD-related inpatient procedures and emergency room visits plus the added monetary losses attributed to productivity which is expected to have equaled $31,517 in 2021. It should be noted that the financial burden per capita highly varies and depends on the severity of the event. Many CAD-attributed medical procedures cost more than the reported average and productivity losses can be much greater, especially for the younger individuals within the target population.

Given an expected compound annual population growth rate of 2.0% and an average inflation rate of 2.7% during the forecast period of 2022 to 2030, it is expected that the total expected direct medical expenditures on all CAD-related events for all U.S. adults aged 55 and older will exceed $608.9 billion by 2030. This equates to a mean per person expenditure on CAD-related inpatient procedures and emergency room visits of $38,455 in 2030, given an expected population of 120 million Americans aged 55 and older with CAD.

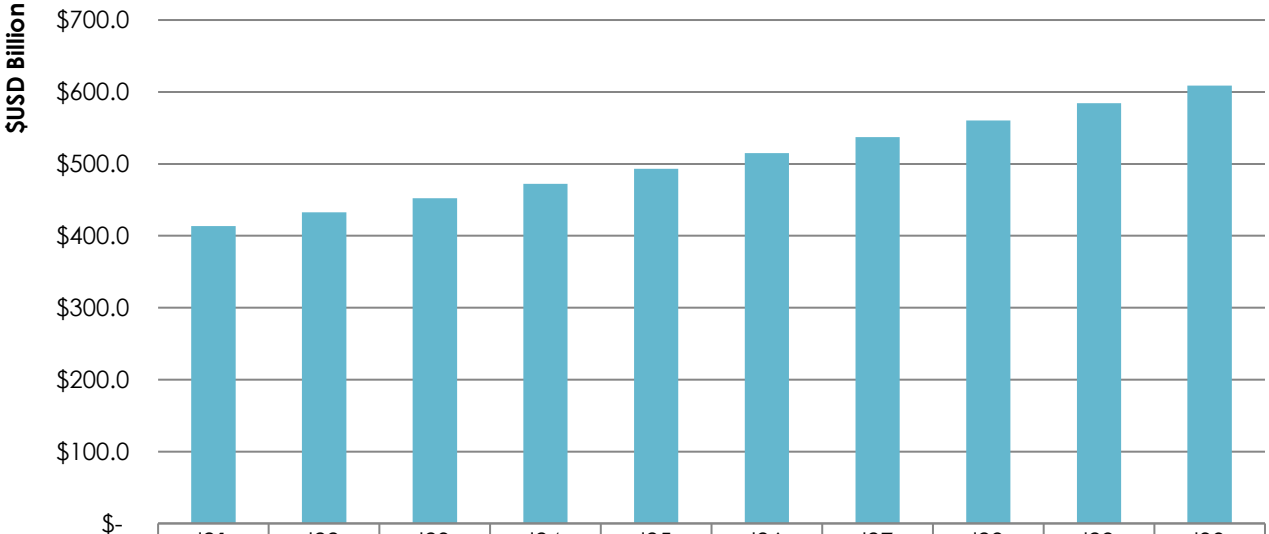
Chart 2. Average Health Care Losses and Productivity Losses per Coronary Artery Disease Event, Thousand $USD per Event, United States, 2020-2030



	'21	'22	'23	'24	'25	'26	'27	'28	'29	'30
Productivity	$3.04	$3.11	$3.18	$3.25	$3.32	$3.39	$3.47	$3.55	$3.63	$3.71
Pharma	$2.21	$2.26	$2.31	$2.37	$2.42	$2.47	$2.53	$2.58	$2.64	$2.70
Medical	$26.26	$26.85	$27.45	$28.06	$28.69	$29.33	$29.98	$30.65	$31.34	$32.04
Total	$31.52	$32.22	$32.94	$33.68	$34.43	$35.20	$35.98	$36.78	$37.61	$38.45

Source: Agency for Healthcare Research and Quality. Medical Expenditure Panel Survey (MEPS)., US Census, and Frost & Sullivan analysis

Chart 3. Total Population Health Care Losses and Productivity Losses Attributed to Coronary Artery Disease, $USD Billion, United States, 2020-2030



	'21	'22	'23	'24	'25	'26	'27	'28	'29	'30
Total	$413.63	$432.58	$452.17	$472.41	$493.34	$514.96	$537.30	$560.38	$584.23	$608.86

Source: Agency for Healthcare Research and Quality. Medical Expenditure Panel Survey (MEPS)., US Census, and Frost & Sullivan analysis

Table 2. Population Health Care Losses and Productivity Losses Attributed to Coronary Artery Disease, $USD Billion, United States, 2020-2030

Year	CAD, Cost of Medical ($ per Event Case)	CAD, Cost of Pharma ($ per Event Case)	CAD, Loss in Productivity ($ per Event Case)	CAD, Cost per Event Case ($ per Event Case)	CAD, Total Population Cost ($ billion)
2021	$26,265	$2,214	$3,038	$31,517	$413.63
2022	$26,851	$2,263	$3,106	$32,220	$432.58
2023	$27,450	$2,314	$3,176	$32,940	$452.17
2024	$28,063	$2,365	$3,246	$33,675	$472.41
2025	$28,690	$2,418	$3,319	$34,427	$493.34
2026	$29,330	$2,472	$3,393	$35,195	$514.96
2027	$29,985	$2,527	$3,469	$35,981	$537.30
2028	$30,654	$2,584	$3,546	$36,784	$560.38
2029	$31,339	$2,642	$3,625	$37,606	$584.23
2030	$32,038	$2,701	$3,706	$38,445	$608.86
Average ('22-'30)	$29,378	$2,476	$3,399	$35,253	$517.36
CAGR	2.2%	2.2%	2.2%	2.2%	4.0%
Cumulative ('22-'30)	--	--	--	--	$4,656.22

Source: Agency for Healthcare Research and Quality. Medical Expenditure Panel Survey (MEPS)., US Census, and Frost & Sullivan analysis

Preventive approaches are critical to the reduction in demand for disease management services. One way to control the burden of CAD costs is to minimize the number of serious events in a target at-risk population. A CAD event may be preventable at least in part, or its seriousness may be meaningfully reduced, by individual patient choices because the development of the disease is believed to be largely a result of lifestyle choices. There is scientific consensus that high blood pressure, high LDL cholesterol, and smoking are leading risk determinants for CAD. High blood pressure and high LDL cholesterol are influenced by lifestyle choices including poor diet, physical inactivity, and alcohol use [7]. On the other hand, choices that have been shown to help to minimize CAD-related events are also available to each patient. Beneficial changes in diet are an example of a step an at-risk individual could take to potentially reduce their chances of experiencing a costly event. Moreover, there is increasing amount of evidence that certain key dietary supplements may reduce a person's odds of experiencing a CAD event.

In the following sections, it will be shown that the use of specific nutritiously dense dietary supplement products have been reported to have positive effects on the cardiovascular health of their users. This may also result in economic benefits in avoided medical costs. Specifically, this chapter explores the possible health and economic effects that could be derived from using four different dietary supplement regimens including omega-3 fatty acids, magnesium, soluble fiber, and

vitamin K2. For each of the four supplements presented here, a description of the scientific literature assessing each supplement's efficacy will be provided as well as projected implications for US healthcare stakeholders in the number of events potentially avoidable with the use of each supplement and economic benefits that could accrue from use of each supplement by an at-risk individual.

Table 3. Coronary Artery Disease Cost Summary Statistics for All U.S. Adults Aged 55 and over, 2021–2030

Metric	'21	CAGR ('21 - '30)	Average ('22 - '30)	Cumulative ('22 - '30)
Total Population, million people	100.97 M	1.96%	111.66 M	--
Population with CAD (people at high risk of experiencing an event), million people	13.12 M	2.11%	14.63 M	--
Event rate—percent of the high-risk population diagnosed with CAD, %	13.0%	0.15%	13.1%	--
Direct cost of CAD, medical service utilization, $USD per Case	$26,265	2.23%	$29,378	--
Direct cost of CAD, pharmaceutical utilization, $USD per Case	$2,214	2.23%	$2,476	--
Indirect Cost of CAD, productivity losses, $USD per Case	$3,038	2.23%	$3,399	--
Total cost of CAD, $USD per Case	$31,517	2.23%	$35,253	--
Total target population cost of CAD, $USD billion	$413.63 B	4.39%	$517.36 B	$4,656.22 B
Price inflation rate, %	6.95%	--	2.23%	

Source: Centers for Disease Control and Prevention, Agency for Healthcare Research and Quality. Medical Expenditure Panel Survey (MEPS)., US Census, and Frost & Sullivan analysis

Omega-3

Literature Review

Omega-3 fatty acids are one of the most well-researched dietary supplement ingredients available and one of those with the most evidence for the support of cardiovascular health. Omega-3 fatty acids are a class of polyunsaturated fatty acids primarily found in marine sources such as fish and algae as well as certain plants. The marine omega-3s eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are the ones most studied in the context of many health conditions, including CAD. Past research has shown that omega-3 EPA improves the cardio-metabolic profiles of users [12]. The American Heart Association (AMA) recommends that patients with documented CAD consume about 1,000 mg per day of a combination of EPA and DHA, preferably from fish sources, and the AMA recommends that 2 to 4 grams of EPA and DHA per day be consumed by patients with high triglyceride levels [11]. The U.S Food & Drug Administration has permitted the use of qualified health claims for omega-3 EPA+DHA for coronary heart disease since 2004 and for hypertension since 2019 [204].

A variety of clinical studies have explored the effects of EPA+DHA omega-3s on a variety of CAD outcomes, including mortality, myocardial infarction, and cardiovascular events in general. The strongest evidence may point toward reducing the number of CAD events and lowering triglyceride levels. In 2013, a meta-analysis of 10 qualified studies found that the relative risk reduction of a CHD event for daily users of Omega-3 EPA+DHA was 6.9% [4]. A meta-analysis published in 2020 identified 40 studies with a combined sample size of 135,267 participants that assessed the effects of Omega-3 EPA+DHA on cardiovascular outcomes including myocardial infarction (MI), coronary heart disease (CHD) including CAD events, CVD events, CHD mortality and fatal MI [12]. Of the 40 included studies, 28 studies representing 131,306 participants assessed the effects on the occurrence of CHD events specifically. The researchers found that supplement use was associated with a 10% reduced risk of experiencing a CHD event (RR, 0.90; 95% CI, 0.84 to 0.97) [12]. The average dose size across all of the included studies was 1,221 mg/day of Omega-3 EPA+DHA per day. Table 4 shows a summary of the key statistics derived from the meta-analyses used to derive the potential economic implications from using Omega-3 EPA+DHA dietary supplements to support coronary heart health.

Table 4. Expected Efficacy of Omega-3 EPA+DHA Supplement on CAD-attributed Event Occurrence

Metric	Measure
Relative risk (weighted for intra-study variance) (RR)	0.90 (95% CI: 0.84 to 0.97)
Relative risk reduction (weighted for intra-study variance) (RRR)	10.0% (95% CI: 3.0%-16.0%)
Absolute risk reduction (ARR)	1.3% (95% CI: 0.4%-2.1%)
Number of people needed to treat to avoid one CAD event (NNT), people	77 (95% CI: 48-256)
Estimated number of events that could have been avoided if the entire target population used Omega-3 EPA+DHA in 2022	174,811
Average number of events avoided annually if the entire target population used Omega-3 EPA+DHA, 2022-2030	191,727

Source: Bernasconi et al. 2021, Frost & Sullivan analysis

Economic Implications

After controlling for variability due to sample size, research methodologies and study protocols, and patient population differences among the studies, the calculated relative risk reduction of a CAD-attributed event with the use of Omega-3 EPA+DHA dietary supplements at preventive intake levels were 10.0%. Because it has been projected that 13.43 million people aged 55 and over will experienced a CAD-related event in 2022, or 13.0% of the target population, 77 people (95% CI: 48-256) could have used daily Omega-3 EPA+DHA supplements at preventive amounts to avoid one CAD-related event. This translates to 174,811 potentially avoidable CAD events in 2022 and could represent 191,727 avoided events per year from 2022 to 2030 given current population and disease risk growth expectations.

Consequently, the reduction in health care costs due to CAD-attributed events potentially avoided by patients consuming omega-3 EPA+DHA at protective levels was estimated at $5.63 billion in 2022, given an average CAD-event cost of $32,220 per case. The annual average cost savings from avoided CAD-attributed events could be $6.78 billion per year in total savings from 2022 to 2030 given current population growth, disease risk growth and price inflationary factors.

In order to account for the cost of daily supplement use, the cost of using Omega-3 EPA+DHA supplements were included in the cost savings assessment. Based on the review of the thirty best-selling retail products currently sold through online sales channels including Amazon and Vitamin Shoppe, the median cost of a daily dose of Omega-3 EPA+DHA is approximately $0.39 per day. Given this daily cost requirement, the median annual expected cost of Omega-3 EPA+DHA dietary

supplementation for all U.S. adults aged 55 and over is $144.01 per person per year or $2.31 billion per year for the total population over the period 2022 to 2030. Table 5 provides a summary of the cost of dietary supplementation with Omega-3 EPA+DHA of the entire target population.

Based the estimated cost of Omega-3 EPA+DHA supplementation, the net cost savings expected from reduced health care expenditures in 2022 resulting from avoided CAD-related events is projected to be $3.70 billion in 2022 or $4.47 billion per year in net savings during the period 2022 to 2030. Table 6 reports the economic implications of the systematic review finding of the beneficial use of Omega-3 EPA+DHA supplements to support cardiovascular health.

Table 5. Omega-3 EPA+DHA Cost Savings Analysis: Summary Results—Cost of Dietary Supplementation of the Target Population, 2022-2030

Metric	Measure
Median daily cost per person of Omega-3 EPA+DHA supplementation at protective daily intake levels, 2022	$0.39
Expected daily median cost per person of Omega-3 EPA+DHA supplementation at protective daily intake levels, 2022-2030	$0.44
Median annual cost per person of Omega-3 EPA+DHA supplementation at protective daily intake levels, 2022	$144.01
Expected annual median cost per person of Omega-3 EPA+DHA supplementation at protective daily intake levels, 2022-2030	$157.65
Total target population cost of Omega-3 EPA+DHA supplementation at protective daily intake levels, 2022	$1.93 B
Total target population cost of Omega-3 EPA+DHA supplementation at protective daily intake levels, 2022-2030	$2.31 B

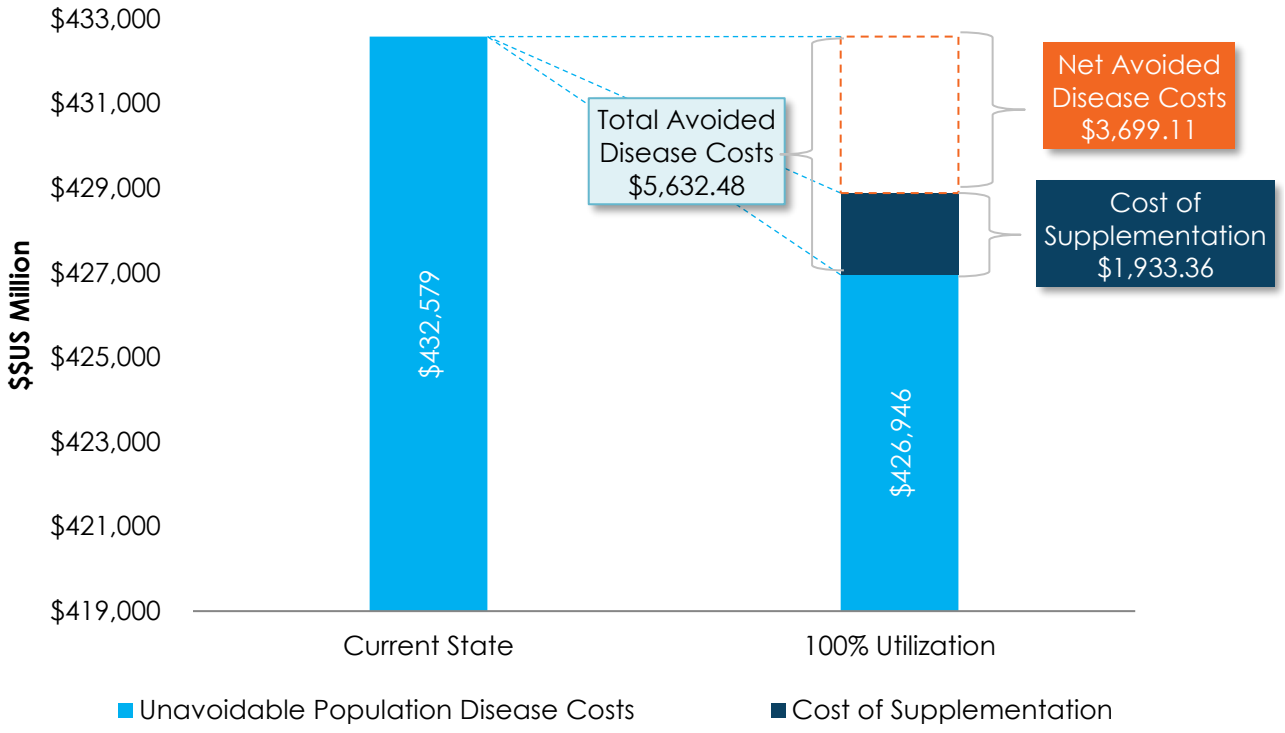
Note: B indicates billion. Source: Frost & Sullivan analysis

Table 6. Omega-3 EPA+DHA Cost Savings Analysis: Summary Results—Avoided Hospital Utilization Expenditures due to Dietary Supplement Intervention, 2022-2030

Metric	Measure
Avoided CAD-attributed hospital utilization expenditures given Omega-3 EPA+DHA supplement intervention per year, 2022	$5.63 B
Average avoided CAD-attributed hospital utilization expenditures given Omega-3 EPA+DHA supplement intervention per year, 2022-2030	$6.78 B
Net avoided CAD-attributed hospital utilization expenditures given Omega-3 EPA+DHA supplement intervention per year, 2022 (includes cost of supplementation)	$3.70 B
Net average avoided CAD-attributed hospital utilization expenditures given Omega-3 EPA+DHA supplement intervention per year, 2022-2030 (includes cost of supplementation)	$4.47 B
Net benefit cost ratio, $ Savings per one dollar spent on dietary supplement	$2.91
Cumulative net target avoided costs, 2022-2030 (NET BENEFITS) ($ billion)	$40.20 B

Note: B indicates billion. Source: Frost & Sullivan analysis

Chart 4. Omega-3 EPA+DHA Cost Savings Analysis: Health Care Cost Savings from the Use of Health Supplement, 2022 Scenario Analysis



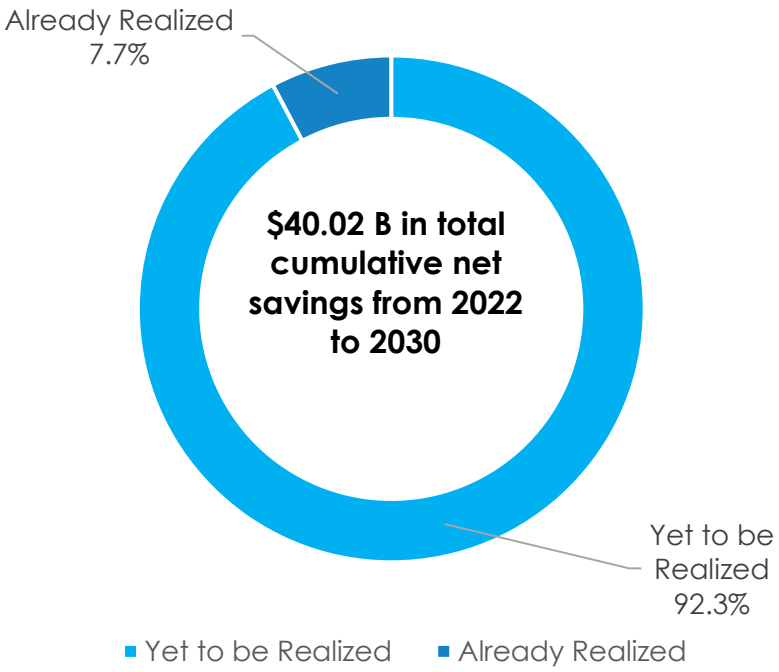
Note: B indicates billion. Source: Frost & Sullivan analysis

The above cost savings results are the maximum savings potential that is obtainable if everyone in the target population (all adults aged fifty-five and older) had not used this product prior to the base year of analysis (e.g., 2022) and then 100% of the population adopted the Omega-3 EPA+DHA regimen in the same year and gained all potential benefits. This assumption was made in order to calculate per capita net benefits which in turn can be used to calculate the net avoided cost savings for the subset of the population yet to use Omega-3 EPA+DHA.

According to the 2021 Council for Responsible Nutrition Consumer Survey on Dietary Supplements conducted by Ipsos Public Affairs, over 40% of US adults aged 55 and older are regular users of dietary supplements and 18**%** of supplement users aged fifty-five and over are regular users of Omega-3 EPA+DHA dietary supplements [152]. This suggests that approximately 7.7% of the total population of US adults aged 55 and older are regular users of Omega-3 EPA+DHA dietary supplements and the remaining 92.3% of the target population 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 EPA+DHA 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.

Thus, it is expected that approximately $3.41 billion of the $3.70 billion in net potential direct savings from avoided CAD hospitalization events because of Omega-3 EPA+DHA dietary supplement intervention is already realized in total expected CAD costs. If utilization rates go unchanged, an average cost savings opportunity of $4.12 billion per year, or $37.09 billion from 2022 to 2030 in cumulative savings, could be lost because of underutilization of Omega-3 EPA+DHA dietary supplements. Hence, it is clear that significant cost savings can be realized from the use of Omega-3 EPA+DHA dietary supplements by the target high-risk population.

Chart 5. Omega-3 EPA+DHA Cost Savings Analysis: Summary Results—Cumulative Net Cost Savings Yet to be Realized due to Avoided Hospital Utilization Expenditures through Dietary Supplement Intervention, 2022-2030



Source: Council for Responsible Nutrition

Table 7. Omega-3 EPA+DHA Cost Savings Analysis: Summary Results—Net Cost Savings Yet to be Realized due to Avoided Hospital Utilization Expenditures through Dietary Supplement Intervention, 2022-2030

Metric	Measure
Net avoided CAD-attributed hospital utilization expenditures given Omega-3 EPA+DHA supplement intervention yet to be realized per year, 2022	$3.41 B
Net average avoided CAD-attributed hospital utilization expenditures given Omega-3 EPA+DHA supplement intervention yet to be realized per year, 2022-2030	$4.12 B
Cumulative net target avoided costs yet realized, 2022-2030 (NET BENEFITS) ($ billion)	$37.09 B

Note: B indicates billion. Source: Frost & Sullivan analysis

Detailed Results

Table 8. Omega-3 EPA+DHA Cost Savings Analysis: Detailed Results—Cost of Dietary Supplementation of the Target Population, 2022-2030

Year	Omega-3 EPA+DHA, Per Capita Daily Cost of Supplementation ($ per day)	Omega-3 EPA+DHA, Per Capita Annual Cost of Supplementation ($ per year)	Omega-3 EPA+DHA, Population Cost of Supplementation ($ billion)
2021	$0.386	$140.79	$1.848
2022	$0.395	$144.01	$1.933
2023	$0.403	$147.22	$2.021
2024	$0.412	$150.92	$2.117
2025	$0.422	$153.87	$2.205
2026	$0.431	$157.30	$2.302
2027	$0.441	$160.81	$2.401
2028	$0.450	$164.85	$2.511
2029	$0.460	$168.07	$2.611
2030	$0.471	$171.83	$2.721
Average ('22-'30)	$0.432	$157.65	$2.314
CAGR	2.24%	2.24%	4.40%
Cumulative ('22-'30)	--	--	$20.823

Source: Frost & Sullivan.

Table 9. Omega-3 EPA+DHA Cost Savings Analysis: Detailed Results—Avoided Hospital Utilization Expenditures due to Dietary Supplement Intervention, 2022-2030

Year	Omega-3 EPA+DHA & CAD, Number of Avoided Events if 100% Utilization by Target User Base (# of Avoided Event Cases)	Omega-3 EPA+DHA & CAD, Total Target Avoided Costs (BENEFITS) ($ billion)	Omega-3 EPA+DHA & CAD, Net Target Avoided Costs (NET BENEFITS) ($ billion)	Omega-3 EPA+DHA, Benefit/Cost Ratio: $Value of Reduced Risk per $1 spent on Supplement ($/$1 supplement spend)
2021	170,585	$5.376	$3.529	$2.91
2022	174,811	$5.632	$3.699	$2.91
2023	179,038	$5.897	$3.877	$2.92
2024	183,266	$6.171	$4.054	$2.91
2025	187,495	$6.455	$4.250	$2.93
2026	191,724	$6.748	$4.446	$2.93
2027	195,955	$7.051	$4.649	$2.94
2028	200,187	$7.364	$4.852	$2.93
2029	204,419	$7.687	$5.076	$2.94
2030	208,652	$8.022	$5.300	$2.95
Average ('22-'30)	191,727	$6.781	$4.467	$2.93
CAGR	2.26%	4.55%	4.62%	0.14%
Cumulative ('22-'30)	1,725,545	$61.028	$40.204	--

Source: Frost & Sullivan.

Table 10. Omega-3 EPA+DHA Cost Savings Analysis: Detailed Results—Net Cost Savings Yet to be Realized due to Avoided Hospital Utilization Expenditures through Dietary Supplement Intervention, 2022-2030

Year	Omega-3 EPA+DHA & CAD, Total Target Avoided Costs Yet Realized (BENEFITS) ($ billion)	Omega-3 EPA+DHA & CAD, Net Target Avoided Costs Yet Realized (NET BENEFITS) ($ billion)
2021	$4.96	$3.26
2022	$5.20	$3.41
2023	$5.44	$3.58
2024	$5.69	$3.74
2025	$5.96	$3.92
2026	$6.23	$4.10
2027	$6.50	$4.29
2028	$6.79	$4.48
2029	$7.09	$4.68
2030	$7.40	$4.89
Average ('22-'30)	$6.26	$4.12
CAGR	4.55%	4.62%
Cumulative ('22-'30)	$56.30	$37.09

Source: Frost & Sullivan.

Magnesium

Literature Review

Magnesium is an essential mineral nutrient typically found in leafy green vegetables, wheat bran, whole grains, and legumes [10]. Magnesium is involved a number of biological processes including cellular signal transduction, adenosine triphosphate (ATP) production, protein synthesis, and bone formation. It is also important in regulating blood pressure and the essential function of the heart.

In 2022, the FDA announced a qualified health claim for products containing magnesium for reduction of blood pressure. It is believed that magnesium affects blood pressure through the renin-angiotensin system, in which it acts as a calcium channel blocker, to reduce vascular resistance and modulate vascular tone and reactivity [14]. This qualified health claim is based on a strong body of scientific evidence showing a link between magnesium use and blood pressure reduction, especially from the last ten years. Thus, for the purposes of this economic analysis, the latest meta-analyses produced by independent researchers were used to derive the expected relative risk reduction of a CHD event given the use of dietary magnesium daily.

Specifically, a 2013 meta-analysis of 16 eligible studies representing 4,319 CAD cases found that the 22% relative risk reduction of a CAD event given the use of dietary magnesium daily (200 mg/day) was statistically significant and clinically meaningful (RR: 0.78; 95% CI: 0.67, 0.92) [15]. This study also deduced that the relative risk reduction of a CAD-attributed event was 30% per 0.2 mmol/L increase in serum magnesium levels (RR: 0.70; 95% CI: 0.56, 0.88) implying that increased intake within safe levels may be correlated with decreased CAD event risk [15].

A more conservative estimate of the relative risk reduction of a CAD event with the daily use of dietary magnesium (median dose size = 368 mg/d) can be derived from the impact of magnesium use on blood pressure (BP) as a biomarker for CAD. Specifically, recent research suggests that the use of dietary magnesium daily for 3 months was associated with a reduction in diastolic BP by 1.78 mm Hg (95% CI, 0.73-2.82) and reduction in systolic BP by 2.00 mm Hg (95% CI, 0.43-3.58) [18]. It was reported in the Framingham Heart Study that a 2.00 mm Hg population-wide diastolic BP reduction was associated with a 6% reduction in the risk of CAD [16, 17]. Therefore, the use of dietary magnesium daily can lead to reduction in risk of experiencing a CAD event 5.3% (RR, 0.947; 95% CI, 0.914 to 0.9781) according to this line of evidence (5.3% = 6.0% x 1.78 mm Hg / 2.00 mm Hg).

Table 11. Expected Efficacy of Magnesium Supplement on CAD-attributed Event Occurrence

Metric	Measure
Reduction in a CAD event risk given a 2.00 mm Hg reduction in diastolic blood pressure [12], [13]	6.0%
Reduction in diastolic blood pressure given use of Magnesium supplements at recommended daily intake levels	1.78 mm Hg (95% CI, 0.73-2.82)
Relative risk (weighted for intra-study variance) (RR)	0.947 (95% CI: 0.915-0.978)
Relative risk reduction (weighted for intra-study variance) (RRR)	5.34% (95% CI: 2.19%-8.46%)
Absolute risk reduction (ARR)	0.69% (95% CI: 0.28%-1.10%)
Number of people needed to treat to avoid one CAD event (NNT), people	144 (95% CI: 91-351)
Estimated number of events that could have been avoided if the entire target population used Magnesium in 2022	93,349
Average number of events avoided annually if the entire target population used Magnesium, 2022-2030	102,382

Source: Zhang et al. 2021 and Frost & Sullivan analysis

Economic Implications

The calculated relative risk reduction of a CAD-attributed event with the use of magnesium dietary supplements at preventive intake levels of 400 mg/day was 5.34% after controlling for variability due to sample size, research methodologies and study protocols, and patient population differences among the studies. Given that 13.43 million people aged 55 and over, or 13.0% of the target population could be expected to experience a CAD-related event in 2022, 144 people (95% CI: 91-351) would have needed to use daily magnesium supplements at preventive levels to avoid one CAD-attributed event. This translates to 93,349 potentially avoidable CAD events in 2022 and an average of 102,382 avoided events per year from 2022 to 2030 given current population and disease risk growth expectations.

The risk reduction effects of daily magnesium intake at protective levels on CAD-attributed event occurrence was calculated as 5.34% if every high-risk person in the target population were to achieve that intake. Consequently, the expected reduction in expenditures in 2022 from avoided CAD-attributed events would have been $3.01 billion in 2022 given an average CAD-event cost of $32,220 per case. Given current population growth, disease risk growth and price inflationary

factors, the expected cost savings derived from avoided CAD-attributed events is $3.62 billion per year from 2022 to 2030.

In order to perform a cost-benefit analysis, the cost of daily use of magnesium supplements was included in the accounting. Based on a review of the thirty best-selling retail magnesium-containing products currently sold through online sales channels including Amazon and Vitamin Shoppe, the median cost of daily supplementation with magnesium at protective levels is approximately $0.22 per day. Given this daily cost, the median annual expected cost of magnesium dietary supplementation for all U.S. adults aged 55 and over would be $81.12 per person per year or $1.30 billion per year for the total population over the period 2022 to 2030. Table 12 provides a summary of the cost of dietary supplementation with magnesium of the entire target population.

Table 12. Magnesium Cost Savings Analysis: Summary Results—Cost of Dietary Supplementation of the Target Population, 2022-2030

Metric	Measure
Median daily cost per person of Magnesium supplementation at protective daily intake levels, 2022	$0.22
Expected daily median cost per person of Magnesium supplementation at protective daily intake levels, 2022-2030	$0.24
Median annual cost per person of Magnesium supplementation at protective daily intake levels, 2022	$81.12
Expected annual median cost per person of Magnesium supplementation at protective daily intake levels, 2022-2030	$88.81
Total target population cost of Magnesium supplementation at protective daily intake levels, 2022	$1.09 B
Total target population cost of Magnesium supplementation at protective daily intake levels, 2022-2030	$1.30 B

Note: B indicates billion. Source: Frost & Sullivan analysis

Based the incurred cost of magnesium dietary supplementation, the net cost savings expected from reduced health care-attributed expenditures in 2022 derived from avoided CAD-attributed events would have been $1.92 billion in 2022 or $2.32 billion per year in net savings during the period 2022 to 2030. Table 13 reports the economic implications of the systematic review finding of the beneficial use of magnesium supplements to support cardiovascular health.

The above results are the maximum potential savings if everyone in the target population (all adults aged 55 and older) had not used this product prior to the base year of analysis (e.g., 2022) and then 100% of that population adopted magnesium supplementation in the same year and gained all potential benefits. This assumption was made in order to calculate per capita net benefits which in

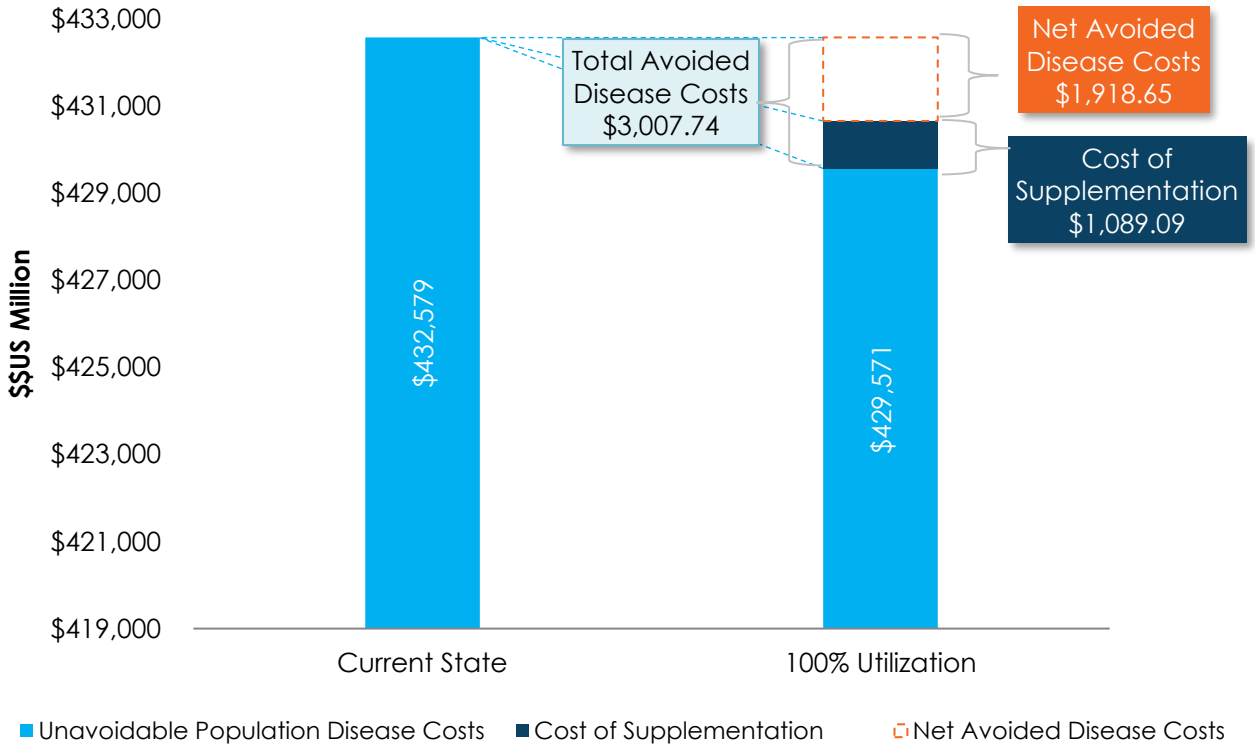
turn can be used to calculate the net potentially avoidable costs for the subset of the population yet to use magnesium.

Table 13. Magnesium Cost Savings Analysis: Summary Results—Avoided Hospital Utilization Expenditures due to Dietary Supplement Intervention, 2022-2030

Metric	Measure
Avoided CAD-attributed hospital utilization expenditures given Magnesium supplement intervention per year, 2022	$3.01 B
Average avoided CAD-attributed hospital utilization expenditures given Magnesium supplement intervention per year, 2022-2030	$3.62 B
Net avoided CAD-attributed hospital utilization expenditures given Magnesium supplement intervention per year, 2022 (includes cost of supplementation)	$1.92 B
Net average avoided CAD-attributed hospital utilization expenditures given Magnesium supplement intervention per year, 2022-2030 (includes cost of supplementation)	$2.32 B
Net benefit cost ratio, $ Savings per one dollar spent on dietary supplement	$2.76
Cumulative net target avoided costs, 2022-2030 (NET BENEFITS) ($ billion)	$20.86 B

Note: B indicates billion. Source: Frost & Sullivan analysis

Chart 7. Magnesium Cost Savings Analysis: Health Care Cost Savings from the Use of Health Supplement, 2022 Scenario Analysis

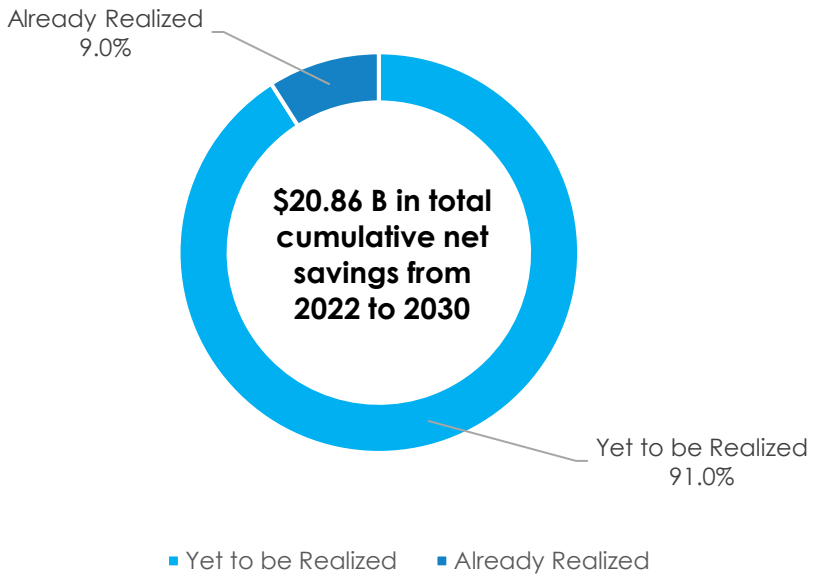


Note: B indicates billion. Source: Frost & Sullivan analysis

Twenty-one percent (21%) of regular dietary supplement users aged 55 and over are users of magnesium dietary supplements according to the Ipsos 2021 Council for Responsible Nutrition Consumer Survey [152]. Given that over 40% of US adults aged 55 and older are regular users of dietary supplements, this implies that that approximately 9.0% of the total population of US adults aged 55 and older are regular users of magnesium the remainder—91%—has yet to realize the potential benefits of the supplements' regular use. Because avoided expenditures and net cost savings are a function of the total number of people in the target population using magnesium dietary supplements, potentially avoidable health care expenditures and net cost savings yet to be realized can be calculated by a proportional adjustment of the total potential avoided expenditures and net cost savings.

Consequently, $1.75 billion of the $1.92 billion in net potential direct savings in 2022 from avoided CAD hospital utilization events because of magnesium dietary supplement intervention may be already realized in total expected CAD costs. If utilization rates go unchanged, an average cost savings opportunity of $2.11 billion over the next eight years could be lost due to underuse of magnesium dietary supplements. Thus, it is expected that there are still significant cost savings possible through the increased usage of magnesium dietary supplements in the target high-risk population.

Chart 8. Magnesium Cost Savings Analysis: Summary Results —Cumulative Net Cost Savings Yet to be Realized due to Avoided Hospital Utilization Expenditures through Dietary Supplement Intervention, 2022-2030



Source: Council for Responsible Nutrition

Table 14. Magnesium Cost Savings Analysis: Summary Results—Net Cost Savings Yet to be Realized due to Avoided Hospital Utilization Expenditures through Dietary Supplement Intervention, 2022-2030

Metric	Measure
Net avoided CAD-attributed hospital utilization expenditures given Magnesium supplement intervention yet to be realized per year, 2022	$1.75 B
Net average avoided CAD-attributed hospital utilization expenditures given Magnesium supplement intervention yet to be realized per year, 2022-2030	$2.11 B
Cumulative net target avoided costs yet realized, 2022-2030 (NET BENEFITS) ($ billion)	$18.98 B

Note: B indicates billion. Source: Frost & Sullivan analysis

Detailed Results

Table 15. Magnesium Cost Savings Analysis: Detailed Results—Cost of Dietary Supplementation of the Target Population, 2022-2030

Year	Magnesium, Daily Cost of Supplementation ($ per day)	Magnesium, Annual Cost of Supplementation ($ per year)	Magnesium, Population Cost of Supplementation ($ billion)
2021	$0.217	$79.31	$1.041
2022	$0.222	$81.12	$1.089
2023	$0.227	$82.93	$1.138
2024	$0.232	$85.02	$1.193
2025	$0.237	$86.68	$1.242
2026	$0.243	$88.61	$1.296
2027	$0.248	$90.59	$1.353
2028	$0.254	$92.87	$1.415
2029	$0.259	$94.68	$1.471
2030	$0.265	$96.79	$1.533
Average ('22-'30)	$0.243	$88.81	$1.303
CAGR	2.24%	2.24%	4.40%
Cumulative ('22-'30)	--	--	$11.730

Source: Frost & Sullivan.

Table 16. Magnesium Cost Savings Analysis: Detailed Results— Magnesium Cost Savings Analysis: Summary Results—Avoided Hospital Utilization Expenditures due to Dietary Supplement Intervention, 2022-2030

Year	Magnesium & CAD, Number of Avoided Events if 100% Utilization by Target User Base (# of Avoided Event Cases)	Magnesium & CAD, Total Target Avoided Costs (BENEFITS) ($ billion)	Magnesium & CAD, Net Target Avoided Costs (NET BENEFITS) ($ billion)	Magnesium, Benefit/Cost Ratio: $Value of Reduced Risk per $1 spent on Supplement ($/$1 supplement spend)
2021	91,092	$2.871	$1.830	$2.76
2022	93,349	$3.008	$1.919	$2.76
2023	95,606	$3.149	$2.011	$2.77
2024	97,864	$3.296	$2.103	$2.76
2025	100,122	$3.447	$2.205	$2.78
2026	102,381	$3.603	$2.307	$2.78
2027	104,640	$3.765	$2.412	$2.78
2028	106,900	$3.932	$2.518	$2.78
2029	109,160	$4.105	$2.634	$2.79
2030	111,420	$4.284	$2.751	$2.79
Average ('22-'30)	102,382	$3.621	$2.318	$2.78
CAGR	2.26%	4.55%	4.63%	0.14%
Cumulative ('22-'30)	921,441	$32.589	$20.859	

Source: Frost & Sullivan.

Table 17. Magnesium Cost Savings Analysis: Detailed Results—Net Cost Savings Yet to be Realized due to Avoided Hospital Utilization Expenditures through Dietary Supplement Intervention, 2022-2030

Year	Magnesium & CAD, Total Target Avoided Costs Yet to be Realized (BENEFITS) ($ billion)	Magnesium & CAD, Net Target Avoided Costs Yet to be Realized (NET BENEFITS) ($ billion)
2021	$2.61	$1.66
2022	$2.74	$1.75
2023	$2.86	$1.83
2024	$3.00	$1.91
2025	$3.14	$2.01
2026	$3.28	$2.10
2027	$3.43	$2.19
2028	$3.58	$2.29
2029	$3.73	$2.40
2030	$3.90	$2.50
Average ('22-'30)	$3.29	$2.11
CAGR	4.55%	4.63%
Cumulative ('22-'30)	$29.65	$18.98

Source: Frost & Sullivan.

Soluble Fiber

Literature Review

Hypercholesterolemia is defined as the occurrence of higher concentrations of low-density lipoprotein (LDL) cholesterol and lower concentrations of functional high-density lipoprotein (HDL) cholesterol, which is correlated to a higher risk of coronary heart disease because of the promotion of plaque development in arteries. Essentially, when too much LDL cholesterol accumulates in arteries, it can cause blockage and increase the risk of a heart attack or stroke [19]. According to the CDC, more than 38% of all U.S. adults have high LDL cholesterol [20].

It is established that diets low in saturated fat and cholesterol are associated with lower LDL cholesterol levels and foods high in soluble fiber help to lower blood LDL cholesterol levels because the indigestible fiber acts as a binder to cholesterol which in turn allows for easier passing of excess cholesterol and prevents it from being absorbed into the blood stream [23]. Dietary fiber is a general term that includes both insoluble and soluble fiber, both of which provide health benefits through nutrition [10]. Soluble fiber from intrinsic sources includes grain, vegetables, and pulses but can be isolated from intrinsic sources and added to other foods. The FDA has authorized health claims for soluble fibers from certain foods, including psyllium husk and beta-glucan from oat and barley and reduced risk of coronary heart disease [208].

It can be followed that any intervention, including dietary supplementation with soluble fiber that is shown to reduce a person's LDL cholesterol level, may also help reduce the odds of experiencing a costly CAD event. According to the National Institutes of Health, a 1% reduction in LDL cholesterol level by any means can reduce the average risk for hard CAD events (myocardial infarction and CAD death) by approximately 1% [22]. Also, 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 cholesterol reduction of 0.51 mmol/L to 1.07 mmol/L [23]. This suggests that a mean risk reduction of 28% to 21% per 1.0 mmol/L reduction in LDL cholesterol or a relative risk reduction of 0.74% to 1.56% given a 1 mg/dL reduction in LDL cholesterol levels. These findings support the findings from a 2007 meta-analysis on the effects of LDL cholesterol concentration reduction on the risk of coronary artery disease. This study deduced that a 1 mmol/L (38.7 mg/dl) reduction in LDL cholesterol provided a 26.6% decrease in the relative risk of experiencing any CHD-related event and a 28.0% decrease in the relative risk of a CHD-attributed death [24].

For the purposes of this economic analysis, the latest meta-analyses produced by independent researchers were cited and used to derive the expected relative risk reduction of a CHD event given the use of dietary soluble fiber daily. This approach was adopted because the clinical research on

soluble fiber and its role in reducing LDL cholesterol levels is strong and a number of recent independent meta-analyses have been conducted supporting this finding. For example, a 2016 meta-analysis of 14 eligible studies (n = 615) exploring the benefits of using barley-based beta-glucan fiber found that using 6.5 to 6.9 grams per day for 4 weeks significantly reduced LDL cholesterol levels (weighted mean difference: -0.25 mmol; 95% CI: -0.30, -0.20) [25]. Also from 2016, researchers at the Cochrane Library conducted a systematic review and identified 12 high quality studies (n = 642) specifically focused on soluble fiber found that its use significantly reduced LDL cholesterol levels (weighted mean difference: -0.14 mmol; 95% CI: -0.23, -0.05) [26]. For the purposes of deriving the expected relative risk reduction of a CAD event a soluble fiber user can expect, the findings of the Cochrane Library meta-analysis were used for the calculations.

It can be shown that the relative risk of a CAD event given the use of soluble fiber can be calculated if we know the relative risk of a CAD event given a 1 mmol/L (38.7 mg/dL) reduction in LDL cholesterol and the expected reduction in LDL cholesterol baseline levels given the use of an LDL cholesterol lowering protective regimen using the following equation:

1. $RR_x = \left(\frac{RR_{x-1}}{RR_x}\right)^{\delta}$

where $\frac{RR_{x-1}}{RR_x}$ is the relative risk of a CHD event given a 1 mmol/L reduction in LDL cholesterol and δ is the expected reduction in LDL cholesterol baseline levels given the use of soluble fiber [24]. As stated above, according to the Gould et al. meta-analysis of the effects of lowering cholesterol on the risk of experiencing a CAD medical event, the relative risk of experiencing a CAD event is reduced by 26.6% for every 1 mmol/L reduction in LDL cholesterol [27]. Furthermore, we know that the estimated mean reduction in LDL cholesterol given use of soluble fiber from the most recent Cochrane Review, so we can let δ = 0.14 mmol/L. Thus, the use of soluble fiber daily can lead up to a 4.24% reduced risk of experiencing a CAD event (RR, 0.9576; 95% CI, 0.9313 to 0.9847). Table 18 reports the aggregated expected effect size of soluble fiber use on cardiovascular event risk.

Table 18. Expected Efficacy of Soluble Fiber on CAD-attributed Event Occurrence

Metric	Measure
Reduction in a CAD event risk given a 1 mmol/L reduction in LDL cholesterol	26.6%
Reduction in LDL cholesterol given use of Soluble Fiber at recommended daily intake levels	0.14 mmol/L (95% CI, 0.05-0.23)
Relative risk (weighted for intra-study variance) (RR)	0.958 (95% CI: 0.931-0.985)
Relative risk reduction (weighted for intra-study variance) (RRR)	4.24% (95% CI: 1.53%-6.87%)
Absolute risk reduction (ARR)	0.55% (95% CI: 0.20%-0.89%)
Number of people needed to treat to avoid one CAD event (NNT), people	181 (95% CI: 112-501)
Estimated number of events that could have been avoided if the entire target population used Soluble Fiber in 2022	74,068
Average number of events avoided annually if the entire target population used Soluble Fiber, 2022-2030	81,236

Source: Ho et al. 2016, Hartley et al. 2016, Gould et al. 2007 and Frost & Sullivan analysis

Economic Implications

The calculated relative risk reduction of a CAD-attributed event given the use of Soluble Fiber dietary supplements at the preventive intake levels was 4.24% 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 13.43 million people aged 55 and over would have experienced a CAD-related event in 2022, or 13.0% of the target population, 181 people (95% CI: 112-501) would have needed to use Soluble Fiber at the daily preventive levels to avoid one CAD-attributed event. This translates to 74,068 potentially avoidable CAD events that could have been saved in 2022 and an average of 81,236 avoided events per year from 2022 to 2030 given current population and disease risk growth expectations.

Consequently, the expected reduction in expenditures in 2022 attributed to avoided CAD-attributed events would have been $2.39 billion in 2022 given an average CAD-event cost of $32,220 per case.

Given current population growth, disease risk growth and price inflationary factors, the expected cost savings derived from avoided CAD-attributed events caused by the use of Soluble Fiber at daily protective intake levels is $2.87 billion per year in total savings from 2022 to 2030.

In order to control for the cost of daily supplement use, the cost of daily use of Soluble Fiber ought to be included in the final accounting. Based on the review of the thirty best-selling retail products currently sold through online sales channels, the median cost of a daily dose of Soluble Fiber is approximately $0.24 per day. Given this daily cost requirement, the median annual expected cost of Soluble Fiber dietary supplementation for all U.S. adults aged 55 and over would be $95.62 per person per year or $1.40 billion per year for the total population over the period 2022 to 2030. Table 19 provides a summary of the cost of dietary supplementation with Soluble Fiber of the entire target population.

Table 19. Soluble Fiber Cost Savings Analysis: Summary Results—Cost of Dietary Supplementation of the Target Population, 2022-2030

Metric	Measure
Median daily cost per person of Soluble Fiber at protective daily intake levels, 2022	$0.24
Expected daily median cost per person of Soluble Fiber at protective daily intake levels, 2022-2030	$0.26
Median annual cost per person of Soluble Fiber at protective daily intake levels, 2022	$87.34
Expected annual median cost per person of Soluble Fiber at protective daily intake levels, 2022-2030	$95.62
Total target population cost of Soluble Fiber at protective daily intake levels, 2022	$1.17 B
Total target population cost of Soluble Fiber at protective daily intake levels, 2022-2030	$1.40 B

Note: B indicates billion. Source: Frost & Sullivan analysis

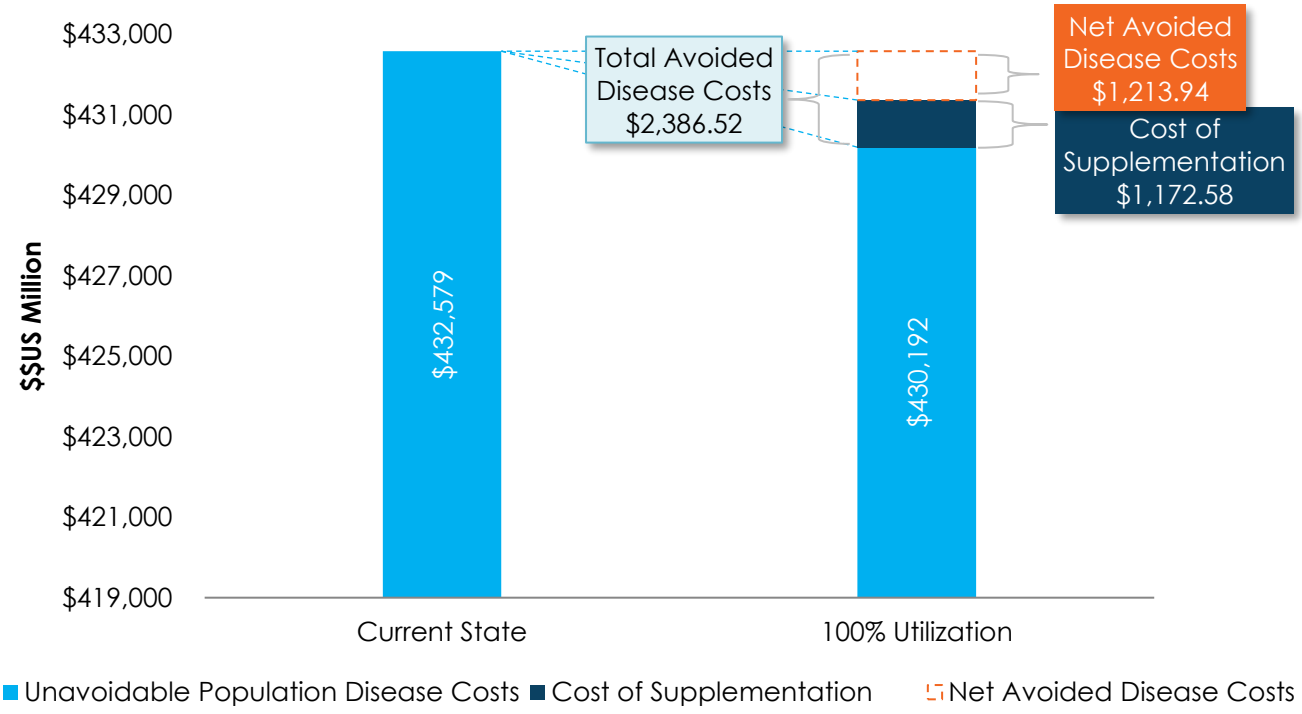
Based the incurred cost of Soluble Fiber dietary supplementation, the net cost savings expected from reduced health care-attributed expenditures in 2022 derived from avoided CAD-attributed events would have been $1.21 billion in 2022 or $1.47 billion per year in net savings and $13.23 billion in cumulative savings during the period 2022 to 2030. Table 20 and Chart 9 reports the economic implications of the systematic review finding of the beneficial use of Soluble Fiber to support cardiovascular health.

Table 20. Soluble Fiber Cost Savings Analysis: Summary Results—Avoided Hospital Utilization Expenditures due to Dietary Supplement Intervention, 2022-2030

Metric	Measure
Avoided CAD-attributed hospital utilization expenditures given Soluble Fiber intervention per year, 2022	$2.39 B
Average avoided CAD-attributed hospital utilization expenditures given Soluble Fiber intervention per year, 2022-2030	$2.87 B
Net avoided CAD-attributed hospital utilization expenditures given Soluble Fiber intervention per year, 2022 (includes cost of supplementation)	$1.21 B
Net average avoided CAD-attributed hospital utilization expenditures given Soluble Fiber intervention per year, 2022-2030 (includes cost of supplementation)	$1.47 B
Net benefit cost ratio, $ Savings per one dollar spent on dietary supplement	$2.04
Cumulative net target avoided costs, 2022-2030 (NET BENEFITS) ($ billion)	$13.23 B

Note: B indicates billion. Source: Frost & Sullivan analysis

Chart 9. Soluble Fiber Cost Savings Analysis: Health Care Cost Savings from the Use of Health Supplement, 2022 Scenario Analysis



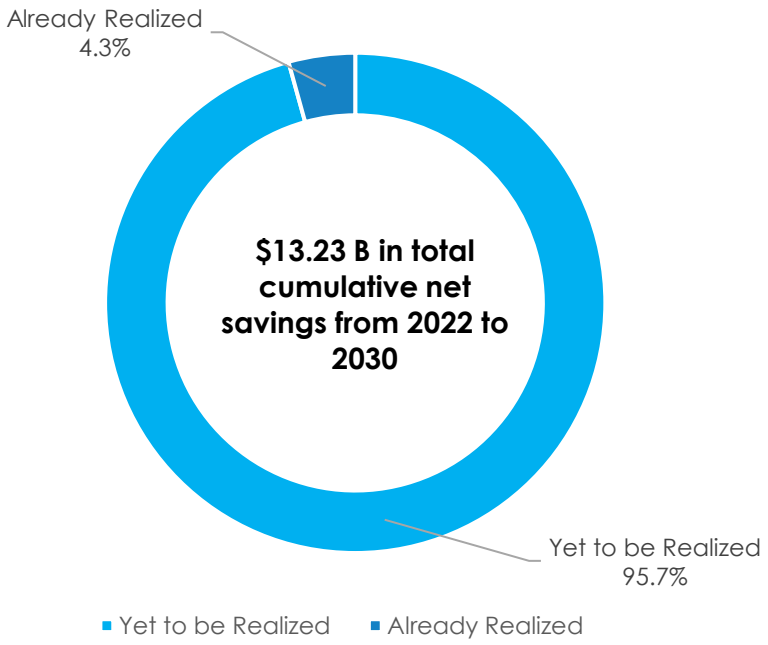
Note: B indicates billion. Source: Frost & Sullivan analysis

The above cost savings results are the maximum savings potential that is obtainable if everyone in the target population (all adults aged 55 and older) had not used this product prior to the base year of analysis (e.g., 2022) and then 100% of the population adopted the soluble fiber regimen in the same year and gained all potential benefits. This assumption was made in order to calculate per capita net benefits which in turn can be used to calculate the net avoided cost savings for the subset of the population yet to use Soluble Fiber.

According to the 2021 Council for Responsible Nutrition Consumer Survey on Dietary Supplements conducted by Ipsos Public Affairs, over 40% of US adults aged 55 and older are regular users of dietary supplements and approximately 10% of supplement users aged 55 and over are regular users of Soluble Fiber dietary supplements [152]. This implies that approximately 4.3% of the total population of US adults aged 55 and older are regular users of Soluble Fiber dietary supplements and the remaining 95.7% of the target population 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 Soluble Fiber 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.

Thus, it is expected that approximately $1.16 billion of the $1.21 billion in net potential direct savings from avoided CAD hospital utilization events because of Soluble Fiber dietary supplement intervention is yet to be realized in total expected CAD costs. If utilization rates go unchanged, an average cost savings opportunity of $1.41 billion per year, or $12.66 billion from 2022 to 2030 in cumulative savings, could be lost because of underutilization of Soluble Fiber dietary supplements. Hence it is expected that there are still significant cost savings yet be realized through the increased usage of Soluble Fiber dietary supplements among the high-risk target population.

Chart 10. Soluble Fiber Cost Savings Analysis: Summary Results—Cumulative Net Cost Savings Yet to be Realized due to Avoided Hospital Utilization Expenditures through Dietary Supplement Intervention, 2022-2030



Source: Council for Responsible Nutrition

Table 21. Soluble Fiber Cost Savings Analysis: Summary Results—Net Cost Savings Yet to be Realized due to Avoided Hospital Utilization Expenditures through Dietary Supplement Intervention, 2022-2030

Metric	Measure
Net avoided CAD-attributed hospital utilization expenditures given Soluble Fiber intervention yet to be realized per year, 2022	$1.16 B
Net average avoided CAD-attributed hospital utilization expenditures given Soluble Fiber intervention yet to be realized per year, 2022-2030	$1.41 B
Cumulative net target avoided costs yet realized, 2022-2030 (NET BENEFITS) ($ billion)	$12.66 B

Note: B indicates billion. Source: Frost & Sullivan analysis

Detailed Results

Table 22. Soluble Fiber Cost Savings Analysis: Detailed Results—Cost of Dietary Supplementation of the Target Population, 2022-2030

Year	Soluble Fiber, Daily Cost of Supplementation ($ per day)	Soluble Fiber, Annual Cost of Supplementation ($ per year)	Soluble Fiber, Population Cost of Supplementation ($ billion)
2021	$0.23	$85.39	$1.121
2022	$0.24	$87.34	$1.173
2023	$0.24	$89.29	$1.226
2024	$0.25	$91.53	$1.284
2025	$0.26	$93.32	$1.337
2026	$0.26	$95.40	$1.396
2027	$0.27	$97.53	$1.456
2028	$0.27	$99.98	$1.523
2029	$0.28	$101.94	$1.584
2030	$0.29	$104.21	$1.650
Average ('22-'30)	$0.26	$95.62	$1.403
CAGR	2.24%	2.24%	4.40%
Cumulative ('22-'30)	--	--	$12.629

Source: Frost & Sullivan.

Table 23. Soluble Fiber Cost Savings Analysis: Detailed Results—Avoided Hospital Utilization Expenditures due to Dietary Supplement Intervention, 2022-2030

Year	Soluble Fiber & CAD, Number of Avoided Events if 100% Utilization by Target User Base (# of Avoided Event Cases)	Soluble Fiber & CAD, Total Target Avoided Costs (BENEFITS) ($ billion)	Soluble Fiber & CAD, Net Target Avoided Costs (NET BENEFITS) ($ billion)	Soluble Fiber, Benefit/Cost Ratio: $Value of Reduced Risk per $1 spent on Supplement ($/$1 supplement spend)
2021	72,278	$2.278	$1.157	$2.03
2022	74,068	$2.387	$1.214	$2.04
2023	75,859	$2.499	$1.273	$2.04
2024	77,651	$2.615	$1.331	$2.04
2025	79,443	$2.735	$1.398	$2.05
2026	81,235	$2.859	$1.463	$2.05
2027	83,027	$2.987	$1.531	$2.05
2028	84,820	$3.120	$1.597	$2.05
2029	86,614	$3.257	$1.674	$2.06
2030	88,407	$3.399	$1.748	$2.06
Average ('22-'30)	81,236	$2.873	$1.470	$2.05
CAGR	2.26%	4.55%	4.69%	0.14%
Cumulative ('22-'30)	731,125	$25.858	$13.229	

Source: Frost & Sullivan.

Table 24. Soluble Fiber Cost Savings Analysis: Detailed Results—Net Cost Savings Yet to be Realized due to Avoided Hospital Utilization Expenditures through Dietary Supplement Intervention, 2022-2030

Year	Soluble Fiber & CAD, Total Target Avoided Costs Yet to be Realized (BENEFITS) ($ billion)	Soluble Fiber & CAD, Net Target Avoided Costs Yet to be Realized (NET BENEFITS) ($ billion)
2021	$2.18	$1.11
2022	$2.28	$1.16
2023	$2.39	$1.22
2024	$2.50	$1.27
2025	$2.62	$1.34
2026	$2.74	$1.40
2027	$2.86	$1.47
2028	$2.99	$1.53
2029	$3.12	$1.60
2030	$3.25	$1.67
Average ('22-'30)	$2.75	$1.41
CAGR	4.55%	4.69%
Cumulative ('22-'30)	$24.75	$12.66

Source: Frost & Sullivan.

Vitamin K2

Literature Review

Vitamin K is a fat-soluble vitamin found naturally in green leafy vegetables, fermented foods, and animal products and the nutrient plays a vital role in blood clotting, bone metabolism, and regulating blood calcium levels [10]. Specifically, Vitamin K is essential for the synthesis of proteins belonging to the γ-carboxyglutamic acid (Gla) protein family. Gla proteins formed in the liver, such as II (prothrombin), VII, IX, and X, play a vital role as procoagulants in hemostasis and prevent bleeding [28]. Other Gla proteins synthesized in the liver, such as Protein C, S, and Z, act as anticoagulants in hemostasis, which inhibits blood clotting. Gla proteins synthesized in tissues include osteocalcin, matrix Gla protein (MGP), and growth-arrest sequence 6 protein (Gas6), which play key functions in maintaining bone strength, arterial calcification inhibition, and cell growth regulation, respectively.

Vitamin K2, also called menaquinones, is a type of vitamin K and is a group of compounds with unsaturated side chains of varying length (chain lengths of 4 to 13 isoprenyl units) [28]. Menaquinone-4 (MK-4), also called menatetrenone, is a short chain vitamin K2 found in animal products such as meat, cheese, and eggs [28]. Longer chain menaquinones such as MK-7, MK-8, MK-9 or higher are found in fermented foods such as cheese, curd, and sauerkraut. MK-7 is found in exceptionally high concentrations in the traditional Japanese food natto [28].

Vitamin K2's role in maintaining health is multifaceted and a growing area of research. Apart from higher bioavailability, several clinical studies show how vitamin K2 serves to improve bone and cardiovascular health. Specifically, it is known that vitamin K2 has a role in both minimizing coronary artery calcium accumulation and increasing calcium content in bone. Specifically, vitamin K2 helps our bodies better distribute and regulate calcium and thus has both heart health and bone health benefits [29]. In other words, vitamin K2 has the potential to both lower the risk of CAD events and minimize the development of osteoporosis, and thus minimize the risk of bone fractures later in life.

To infer the expected efficacy of using vitamin K2 on the occurrence of a CAD event, a literature review was conducted in March 2022 that focused on published studies that tested for and quantified the effect of vitamin K2 supplementation on the incidence of CAD-related medical events requiring medical treatment. The goal of this study was to collect a sample of studies that represented the state of all scientific literature on vitamin K2 supplementation. In addition, studies selected for analysis must have tested for a direct causal relationship between the intake of a vitamin K2 dietary supplement regimen and the relative risk of a CAD event. It was preferred that the selected studies were similar in study protocol in an attempt to control likely variances, though this is not always possible due to the nature of it being a young body of research. Specifically, of the various study methods found for vitamin K2 supplementation, randomized controlled trials (RCT)

were preferred because they are designed to directly test for a cause-and-effect relationship between treatment and outcome though prospective cohort studies were also considered because they too tested for similar and comparable hypotheses. Studies were not selected on the basis of the magnitude, direction, or statistical significance of the reported findings.

One hundred twenty-six (126) studies were found in a PubMed search based on the use of "vitamin K2" or "menaquinone" or "; "coronary heart disease" or "coronary artery disease"; and "risk reduction" as filtering keywords. The search was conducted between March 1 and March 31, 2022. Once the set of possible studies were created, each study's title, abstract and results was thoroughly reviewed and assessed to determine whether there was an association between supplement intake and the relative risk or odds ratio of a coronary artery disease event. Specifically, a study was considered qualified for inclusion in the analysis if it tested for a relationship between the intake of a vitamin K2 supplement and the reduction in the odds of a CAD event occurring, independent of the direction of the relationship. Six (6) prospective cohort studies were identified as representative of the vitamin K2 literature and were used to deduce the estimated efficacy of high intake of K2 on reducing CAD-related medical event risk. It should be noted that that there were no RCTs identified that directly assessed the vitamin K2 intervention and CAD events and the relative risk estimated for the cost analysis is based on observational studies. However, a number of RCTs were uncovered that showed a link between vitamin K2 supplement intake and vascular biomarkers [206, 207]. Table 25 shows a description of a selection of included studies in the final meta-analysis.

Researchers began to get a better understanding of the potential benefits of using vitamin K2 menaquinone in 2004 when researchers from the Rotterdam Study first uncovered a possible association with its intake and a reduced risk of experiencing a coronary heart disease event [31]. The researchers used data from the Rotterdam Study which included 4,807 patient subjects as of 1990 to 1993 and who were followed for 7 to 10 years [31]. After assessment using a Cox regression model to derive relative risk, it was found that the relative risk of a coronary heart disease event among the top tertile of subjects was 41% lower compared to the lowest tertile (Relative Risk = 0.59, 95% CI: 0.40-0.86) after controlling traditional risk factors and food intake considerations [31].

Table 25. Vitamin K2 Literature Review: Description of the Qualified Studies

Refe-rence	Author	Year	Daily dose and Study Duration	Event definition
31	Geleijnse *et al.*	2004	More than 32.7 micrograms per day versus less than 21.6 micrograms per day. Patients were followed for 7 to 10 years.	Incident CAD Events
30	Gast *et al.*	2009	More than 36 micrograms per day versus less than 21.6 micrograms per day. Patients were followed for 8.1 +/- 1.6 years.	Hazard Ratio of Experiencing a CAD Event between the High Intake versus Low Intake quartile cohorts
153	Juanola-Falgarona *et al.*	2014	More than 57.5 micrograms per day versus less than 18.4 micrograms per day. Patients were followed for an average of 4.8 years.	Hazard Ratio of Experiencing a CAD Death between the High Intake versus Low Intake quartile cohorts
34	Zwakenberg *et al.*	2017	63.7 ± 11.3 micrograms per day versus 26.2 ± 4.9 micrograms per day. Patients were followed for an average of 16.8 years.	Hazard Ratio of Experiencing a CAD Death between the High Intake versus Low Intake quartile cohorts
32	Haugsgjerd *et al.*	2020	More than 15 (11 to 21) micrograms per day versus less than 24 (21 to 29) micrograms per day. Patients were followed for an average of 11 years.	Hazard Ratio of Experiencing a CAD Event between the High Intake versus Low Intake quartile cohorts
33	Bellinge *et al.*	2021	More than 77 (65 to 296) micrograms per day versus less than 23 (0 to 29) micrograms per day. Patients were followed for an average of 21 years.	Hazard Ratio of Experiencing ASCVD-related hospitalization between the High Intake versus Low Intake quintile cohorts

In 2009, Gast et al. were one of the earliest team of researchers to discover a strong association between high vitamin K2 intake and lower risk of experiencing a coronary heart event [30]. Using data from the Prospect–EPIC cohort study which included 16,057 women free of heart disease age 49 to 70 years old, the researchers followed the cohort for a mean 8.1 years and the researchers counted 480 cases of CHD during that time [30]. At the time, the mean vitamin K2 intake level among the cohort was only 29.1 micrograms per day per person, which is significantly lower than generally recommended today [30]. The researchers used a multivariate Cox proportional hazards model to estimate the hazard ratios and found that the relative risk of experiencing a CAD-event was negatively correlated with vitamin K2 intake after controlling for other traditional risk and dietary factors (Hazard Ratio = 0.91, 95% CI: 0.85-1.00) [30].

Additionally, a prospective cohort study that included 33,289 participants aged 20-70 years was published by Clinical Nutrition in 2017 and showed that high intake of vitamin K2 was correlated with a significant reduction in the risk of CAD (coronary heart disease) [34]. Specifically, those individuals within the high vitamin K2 intake cohort had significantly lower odds of experiencing a CAD-attributed mortality event compared to the low vitamin K2 intake cohort (Hazard Ratio = 0.86, 95% CI: 0.74-1.00) [34].

In 2021, researchers evaluated the resultant relative risk of experiencing an atherosclerotic cardiovascular disease event (hospitalization) given relative vitamin K2 intake levels among 53,372 patients in Denmark and with a median age of 56 from the Danish Diet Cancer and Health Study [33]. In this study, researchers monitored these patients for 17 to 22 years and counted 8,726 atherosclerotic cardiovascular disease related hospitalization [33]. The researchers found that individuals at the highest vitamin K2 intake quintile had a 14% lower risk of atherosclerotic cardiovascular disease hospitalization compared to the lowest vitamin K2 intake quintile (Hazard Ratio = 0.86, 95% CI: 0.81-0.91) [33].

Similarly, researchers evaluated the Hordaland Health Study Cohort study from Norway in 2020 to determine if an association was present between dietary vitamin K intake and the risk of a coronary heart disease event [32]. Two thousand nine hundred and eighty-seven (2,987) men and women aged 46 to 49 from Norway were followed for a median 11 years and the researchers counted 112 CAD event cases [32]. In this study, the researchers found that those individuals in the highest vitamin K2 intake quartile had 48% lower odds of experiencing a CAD event compared to the lowest vitamin K2 intake quartile cohort (Hazard Ratio = 0.52, 95% CI: 0.29-0.94) [32].

There were many other studies that were not included in the final analysis due to differences in reported outcomes and target populations yet still suggest that use of vitamin K2 significantly supports cardiovascular health. For example, Knapen et al. investigated the use of menaquinone vitamin K2 on specific vascular biomarkers that are known to have a link to heart health in 2015 [35]. The researchers divided 240 postmenopausal healthy women free from cardiovascular disease into two groups based on their baseline arterial stiffness (i.e., stiffness index cut-off at 10.8; 50th percentile). The researchers found that use of vitamin K2 over three years had a statistically significant improvement on carotid-femoral pulse-wave velocity (cfPWV) and arterial elasticity among women in the high arterial stiffness group [35]. And in 2020, similar research was conducted exploring the link between utilization of vitamin K2 and specific vascular biomarkers among 243 men and women subjects [36]. The researchers found that women using vitamin K2 for one year had decreased mean uncarboxylated matrix Gla protein (dp-ucMGP) levels from 639 to 450 pmol/L, while in men the decrease was from 681 to 652 pmol/L, suggesting that vitamin K2 intake among women can lead to a significant reduction in age-related vascular stiffening [36].

To deduce the effect of using vitamin K2 on the occurrence of an CAD event, a random-effects meta-analysis model was developed based on the systematic review process developed by DerSimonian and Laird (1986) which is a common approach for deducing the true treatment effect from a set of clinical research citations that varies by sample size, methodologies and study protocols, and patient population dynamics [5, 37]. 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 [5].

Based on applying the random-effects meta-analysis model to the qualified set of clinical studies described in detail above, it is estimated that the relative risk reduction (RRR) of a CAD event, given the preventive daily use of vitamin K2 supplements, is 15.7% (95% CI: 3.2% - 25.0%) after controlling for variance caused by study sample size, research protocols, and patient population differences within each study and among all studies. Given a CAD event risk of 13% among adults aged 55 and older, the number of people that would need to use a vitamin K2 supplement to avoid one CAD event is approximately 49 (95% CI: 31-240) people. In other words, if approximately 49 people used vitamin K2 supplements at daily protective intake levels, one CAD hospitalization event would be avoided among that group. Given an NNT of 49 people, the number of potential avoided events among all U.S. adults aged 55 and over diagnosed with CAD could be an estimated 274,933 avoided events in 2022 and is expected to be an average of 301,539 events per year from 2022 to 2030 given current population and disease risk growth expectations. Table 26 describes the empirical results of the included studies in the final systematic review and Table 27 reports the aggregated expected effect size of vitamin K2 use on cardiovascular event risk.

Table 26. Vitamin K2 Literature Review: Summary of Study Findings

Author	Total sample (N)	Reported Effect Size	95% Low	95% High	Study weight (based on random effects model)
Geleijnse *et al.*	4,807	0.59	0.40	0.86	6.3%
Gast *et al.*	16,057	0.91	0.85	1.00	19.7%
Juanola-Falgarona *et al.*	7,216	0.76	0.44	1.29	4.2%
Zwakenberg *et al.*	33,289	0.86	0.74	1.00	42.8%
Haugsgjerd *et al.*	2,987	0.52	0.29	0.94	5.3%
Bellinge *et al.*	53,372	0.86	0.81	0.91	21.6%

Table 27. Expected Efficacy of Supplement Use Based on Literature Review, vitamin K2

Metric	Measure
Relative risk (weighted for intra-study variance) (RR)	0.84 (95% CI: 0.737-0.966)
Relative risk reduction (weighted for intra-study variance) (RRR)	15.7% (95% CI: 3.2%-25.0%)
Absolute risk reduction (ARR)	2.0% (95% CI: 0.4%-3.2%)
Number of people needed to treat to avoid one CAD event (NNT), people	49 (95% CI: 31-240)
Estimated number of events that could have been avoided if the entire target population used Vitamin K2 in 2022	274,933
Average number of events avoided annually if the entire target population used Vitamin K2, 2022-2030	301,539

Source: Frost & Sullivan analysis

Economic Implications

Given the risk reducing effect of using vitamin K2 on CAD-attributed event occurrence of 15.7%, which is achievable if every high-risk person in the target population were to take vitamin K2 supplements at protective levels daily, the expected reduction in expenditures in 2022 attributed to avoided CAD-attributed events would have been $8.86 billion in 2022 given an average CAD-event cost of $32,220 per case in that year. Given current population growth, disease risk growth and price inflationary factors, the expected cost savings derived from avoided CAD-attributed events caused by the use of vitamin K2 at daily protective intake levels is $10.66 billion per year in total savings from 2022 to 2030.

In order to ensure that all cost considerations are taken into account, the cost of daily use of dietary supplements ought to be included in the final accounting. Based on the review of the best-selling retail products currently sold through online sales channels, the median cost of a daily dose of vitamin K2 is approximately $0.20 per day. Given this daily cost requirement, the median annual expected cost of vitamin K2 dietary supplementation for all U.S. adults aged 55 and over would be $80.85 per person per year or $1.19 billion per year for the total population over the period 2022 to 2030. Table 28 provides a summary of the cost of dietary supplementation with vitamin K2 of the entire target population.

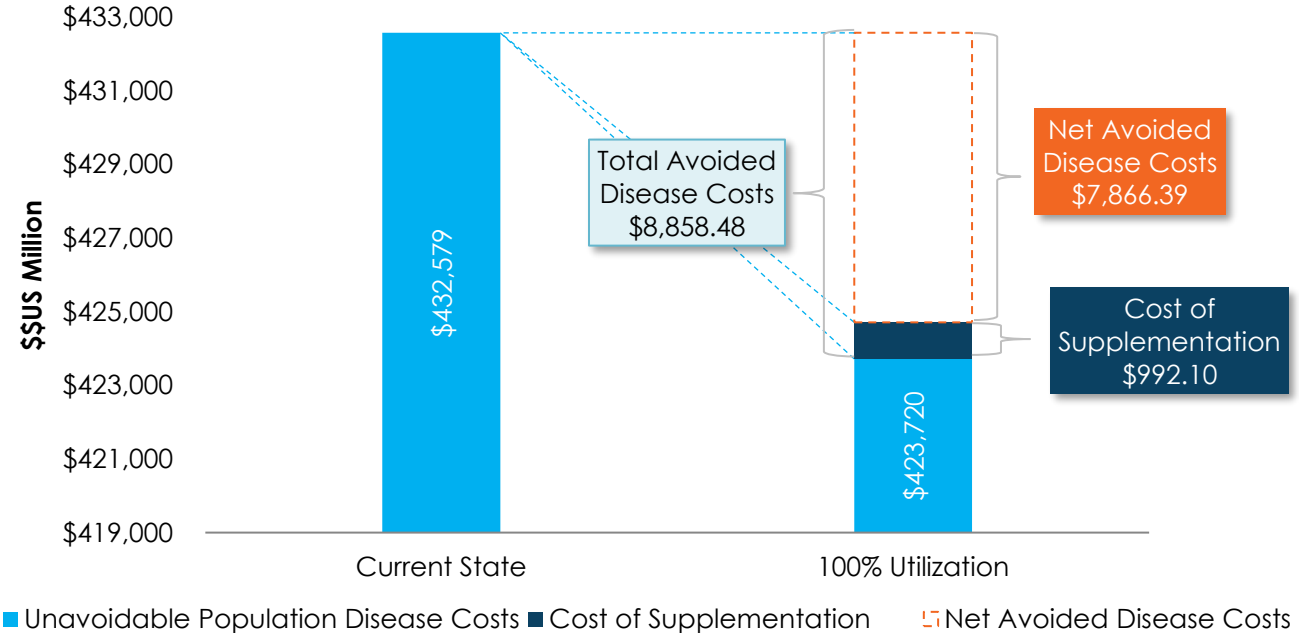
Table 28. Vitamin K2 Cost Savings Analysis: Summary Results—Cost of Dietary Supplementation of the Target Population, 2022-2030

Metric	Measure
Median daily cost per person of Vitamin K2 supplementation at protective daily intake levels, 2022	$0.20
Expected daily median cost per person of Vitamin K2 supplementation at protective daily intake levels, 2022-2030	$0.22
Median annual cost per person of Vitamin K2 supplementation at protective daily intake levels, 2022	$73.90
Expected annual median cost per person of Vitamin K2 supplementation at protective daily intake levels, 2022-2030	$80.85
Total target population cost of Vitamin K2 supplementation at protective daily intake levels, 2022	$0.99 B
Total target population cost of Vitamin K2 supplementation at protective daily intake levels, 2022-2030	$1.19 B

Note: B indicates billion. Source: Frost & Sullivan analysis

Given the incurred cost of vitamin K2 dietary supplementation, the net cost savings expected from reduced health care-attributed expenditures in 2022 from avoided CAD-attributed events would have been $7.87 billion in 2022 or $9.48 billion per year in net savings and $85.30 billion in cumulative net savings during the period 2022 to 2030. Table 29 reports the economic implications of the systematic review finding of the beneficial use of vitamin K2 supplements to support cardiovascular health.

Chart 11. Vitamin K2 Cost Savings Analysis: Health Care Cost Savings from the Use of Health Supplement, 2022 Scenario Analysis



Note: B indicates billion. Source: Frost & Sullivan analysis

Table 29. Vitamin K2 Cost Savings Analysis: Summary Results—Avoided Hospital Utilization Expenditures due to Dietary Supplement Intervention, 2022-2030

Metric	Measure
Avoided CAD-attributed hospital utilization expenditures given Vitamin K2 supplement intervention per year, 2022	$8.86 B
Average avoided CAD-attributed hospital utilization expenditures given Vitamin K2 supplement intervention per year, 2022-2030	$10.66 B
Net avoided CAD-attributed hospital utilization expenditures given Vitamin K2 supplement intervention per year, 2022 (includes cost of supplementation)	$7.87 B
Net average avoided CAD-attributed hospital utilization expenditures given Vitamin K2 supplement intervention per year, 2022-2030 (includes cost of supplementation)	$9.48 B
Net benefit cost ratio, $ Savings per one dollar spent on dietary supplement	$8.93
Cumulative net target avoided costs, 2022-2030 (NET BENEFITS) ($ billion)	$85.30 B

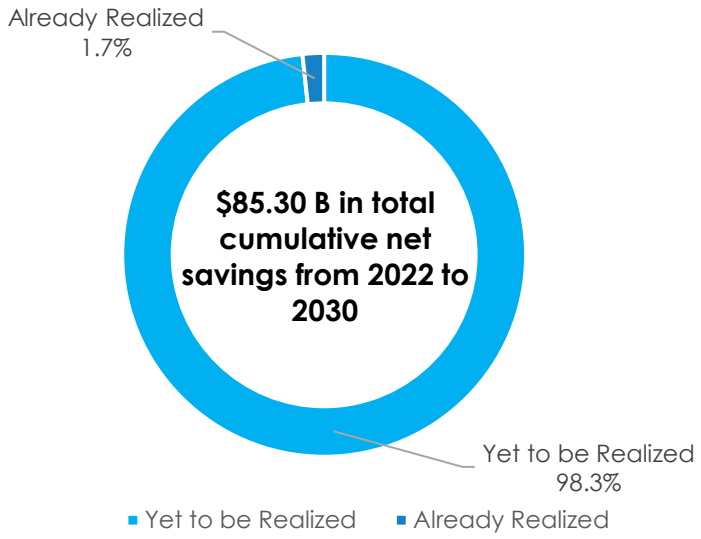
Note: B indicates billion. Source: Frost & Sullivan analysis

The above cost savings results are the maximum savings potential that is obtainable if everyone in the target population (all adults aged 55 and older) had not used this product prior to the base year of analysis (e.g., 2022) and then 100% of the population adopted the vitamin K2 regimen in the same year and gained all potential benefits. This assumption was made in order to calculate per capita net benefits which in turn can be used to calculate the net avoided cost savings for the subset of the population yet to use vitamin K2.

According to the 2021 Council for Responsible Nutrition Consumer Survey on Dietary Supplements conducted by Ipsos Public Affairs, over 40% of US adults aged 55 and older are regular users of dietary supplements and approximately 4% of supplement users aged 55 and over are regular users of vitamin K2 dietary supplements [152]. This implies that approximately 1.7% of the total population of US adults aged 55 and older are regular users of vitamin K2 dietary supplements and the remaining 98.3% of the target population 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 vitamin K2 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.

Thus, it is expected that approximately $7.73 billion of the $7.87 billion in net potential direct savings from avoided CAD hospital utilization events because of vitamin K2 dietary supplement intervention is yet to be realized in total expected CAD costs. If utilization rates go unchanged, an average cost savings opportunity of $9.32 billion per year, or $83.84 billion from 2022 to 2030 in cumulative savings, could be lost because of underutilization of vitamin K2 dietary supplements. Hence it is expected that there are still significant cost savings yet be realized through the increased usage of vitamin K2 dietary supplements among the high-risk target population.

Chart 12. Vitamin K2 Cost Savings Analysis: Summary Results—Cumulative Net Cost Savings Yet to be Realized due to Avoided Hospital Utilization Expenditures through Dietary Supplement Intervention, 2022-2030



Source: Council for Responsible Nutrition

Table 30. Vitamin K2 Cost Savings Analysis: Summary Results—Net Cost Savings Yet to be Realized due to Avoided Hospital Utilization Expenditures through Dietary Supplement Intervention, 2022-2030

Metric	Measure
Net avoided CAD-attributed hospital utilization expenditures given Vitamin K2 supplement intervention yet to be realized per year, 2022	$7.73 B
Net average avoided CAD-attributed hospital utilization expenditures given Vitamin K2 supplement intervention yet to be realized per year, 2022-2030	$9.32 B
Cumulative net target avoided costs yet realized, 2022-2030 (NET BENEFITS) ($ billion)	$83.84 B

Note: B indicates billion. Source: Frost & Sullivan analysis

Detailed Results

Table 31. Vitamin K2 Cost Savings Analysis: Detailed Results—Cost of Dietary Supplementation of the Target Population, 2022-2030

Year	Vitamin K2, Daily Cost of Supplementation ($ per day)	Vitamin K2, Annual Cost of Supplementation ($ per year)	Vitamin K2, Population Cost of Supplementation ($ billion)
2021	$0.20	$72.25	$0.948
2022	$0.20	$73.90	$0.992
2023	$0.21	$75.55	$1.037
2024	$0.21	$77.23	$1.083
2025	$0.22	$78.96	$1.131
2026	$0.22	$80.72	$1.181
2027	$0.23	$82.52	$1.232
2028	$0.23	$84.36	$1.285
2029	$0.24	$86.25	$1.340
2030	$0.24	$88.17	$1.396
Average ('22-'30)	$0.22	$80.85	$1.187
CAGR	2.2%	2.2%	4.4%
Cumulative ('22-'30)	--	--	$10.679

Source: Frost & Sullivan.

Table 32. Vitamin K2 Cost Savings Analysis: Detailed Results—Avoided Hospital Utilization Expenditures due to Dietary Supplement Intervention, 2022-2030

Year	Vitamin K2 & CAD, Number of Avoided Events if 100% Utilization by Target User Base (# of Avoided Event Cases)	Vitamin K2 & CAD, Total Target Avoided Costs (BENEFITS) ($ billion)	Vitamin K2 & CAD, Net Target Avoided Costs (NET BENEFITS) ($ billion)	Vitamin K2, Benefit/Cost Ratio: $Value of Reduced Risk per $1 spent on Supplement ($/$1 supplement spend)
2021	268,287	$8.456	$7.507	$8.92
2022	274,933	$8.858	$7.866	$8.93
2023	281,582	$9.275	$8.238	$8.94
2024	288,231	$9.706	$8.623	$8.96
2025	294,882	$10.152	$9.020	$8.97
2026	301,535	$10.613	$9.432	$8.99
2027	308,188	$11.089	$9.857	$9.00
2028	314,843	$11.581	$10.296	$9.01
2029	321,500	$12.090	$10.750	$9.02
2030	328,157	$12.616	$11.220	$9.03
Average ('22-'30)	301,539	$10.665	$9.478	$8.99
CAGR	2.26%	4.55%	4.57%	2.24%
Cumulative ('22-'30)	2,713,851	$95.981	$85.302	

Source: Frost & Sullivan.

Table 33. Vitamin K2 Cost Savings Analysis: Summary Results—Net Cost Savings Yet to be Realized due to Avoided Hospital Utilization Expenditures through Dietary Supplement Intervention, 2022-2030

Year	Vitamin K2 & CAD, Total Target Avoided Costs Yet to be Realized (BENEFITS) ($ billion)	Vitamin K2 & CAD, Net Target Avoided Costs Yet to be Realized (NET BENEFITS) ($ billion)
2021	$8.31	$7.38
2022	$8.71	$7.73
2023	$9.12	$8.10
2024	$9.54	$8.47
2025	$9.98	$8.87
2026	$10.43	$9.27
2027	$10.90	$9.69
2028	$11.38	$10.12
2029	$11.88	$10.57
2030	$12.40	$11.03
Average ('22-'30)	$10.48	$9.32
CAGR	4.55%	4.57%
Cumulative ('22-'30)	$94.33	$83.84

Source: Frost & Sullivan.

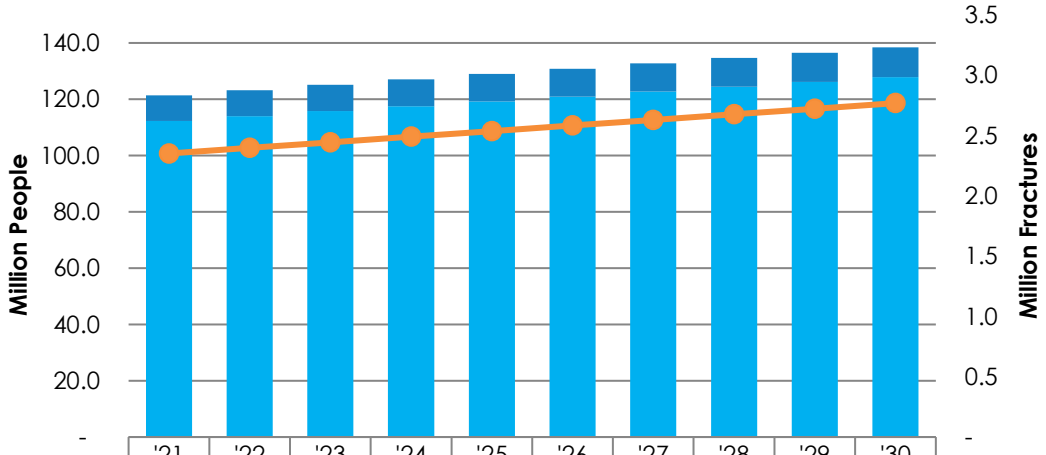
OSTEOPOROSIS AND THE BENEFITS OF USING CALCIUM & VITAMIN D TO REDUCE FRACTURE RISK

The Burden and Social Consequences

Osteoporosis, a metabolic bone disease that causes reduced mineral density and quality of bone, is a significant health and economic burden in the US [38, 39, 40]. During the osteoporotic process, the net rate of bone resorption exceeds that of bone formation and retention, resulting in a decrease in overall bone mass. When the bone mass available for skeletal support falls below the fracture threshold, it is easier to sustain a fracture with a simple fall or little to no trauma to the bone. 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 [43]. These fractures can lead to pain, severe disability, or loss of mobility.

Women are at significantly greater risk of developing osteoporosis after menopause and thus bear a significantly heavier burden, both financially and in terms of reduced quality of life if osteoporosis is allowed to be developed uninhibited. 9.2 million people in the country suffer from osteoporosis with females accounting for over 87% of cases [41,42]. More than a quarter of the osteoporotic population (26.1%) will experience a bone fracture as a result of poor bone quality and reduced mineral density with a predicted 2.40 million fractures occurring among osteoporotic individuals aged 50 and older in 2022 [44].

Chart 13. Target Population Size and Prevalence of Osteoporosis, United States, 2020-2030



	'21	'22	'23	'24	'25	'26	'27	'28	'29	'30
All Adults	121.4	123.3	125.2	127.1	129.0	130.9	132.8	134.7	136.6	138.5
Osteoporotic Pop	9.0	9.2	9.4	9.5	9.7	9.9	10.0	10.2	10.4	10.6
Heathy Adults	112.3	114.1	115.8	117.5	119.3	121.0	122.7	124.4	126.2	127.9
Fractures (million)	2.4	2.4	2.4	2.5	2.5	2.6	2.6	2.7	2.7	2.8

Source: Kanis 2012, Wright et al. 2014, Weaver et al. 2019, US Census, and Frost & Sullivan analysis

Table 34. Target Population Size and Prevalence of Osteoporosis, United States, 2020-2030

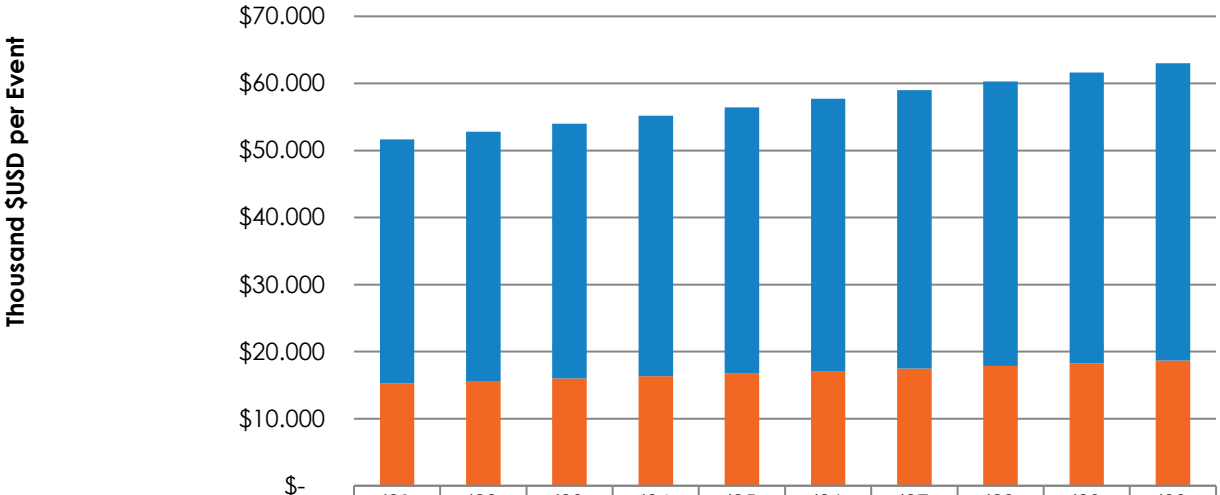
Year	Total Population, age 50 and older (million people)	Population, Diagnosed with Osteoporosis (million people)	Osteoporosis, Fractures (million fractures)
2021	121.35	9.03	2.35
2022	123.25	9.20	2.40
2023	125.16	9.37	2.44
2024	127.06	9.54	2.49
2025	128.96	9.71	2.54
2026	130.86	9.88	2.58
2027	132.76	10.05	2.63
2028	134.66	10.21	2.68
2029	136.56	10.38	2.72
2030	138.46	10.55	2.77
Average ('22-'30)	130.86	9.88	2.58
CAGR	1.5%	1.7%	1.8%

Source: Kanis 2012, Wright et al. 2014, Weaver et al. 2019, US Census, and Frost & Sullivan analysis

Every osteoporotic fracture result in a series of financial burdens that are a consequence of the event and includes expensive direct medical costs such as cost of hospitalization, cost of surgery, treatment pharmaceuticals, ambulatory services, emergency room visits and other hard costs tied to treating a medical event and indirect costs related to post-event disease management and the consequences of disability (e.g., productivity losses). A 2014 study of Medicare claims found that the direct and indirect economic impact per hip fracture on the US healthcare system was over $50,000 per case [45]. 70% of this cost was credited to costs tied to post-fracture disability [45].

Also, healthcare cost data related to preventing, treating, and managing the physical burden of osteoporosis for the entire US population was provided by Weaver et al 2019 [44]. This study reported that the direct cost of osteoporosis was over $28 billion per year given a per-person hospital-related cost of fracture of $12,197 in 2016 [44]. The direct cost per-person hospital-related cost of fracture included room and bed, medical supplies, operating room and laboratory expenditures, pharmaceuticals, and other hospital fees. An estimate for the direct cost of treating a given fracture in 2018 was determined by extrapolating to current 2018 dollars using a conservative inflationary rate of 1.5% per year.

Chart 14. Average Health Care Costs and Productivity Losses per Osteoporosis Event, Thousand $USD per Event, United States, 2020-2030



	'21	'22	'23	'24	'25	'26	'27	'28	'29	'30
Indirect Medical, Pharma, and Productivity Losses	$36.36	$37.18	$38.01	$38.85	$39.72	$40.61	$41.52	$42.44	$43.39	$44.36
Direct Medical Costs	$15.30	$15.64	$15.99	$16.34	$16.71	$17.08	$17.46	$17.85	$18.25	$18.66
Total	$51.66	$52.81	$53.99	$55.20	$56.43	$57.69	$58.98	$60.29	$61.64	$63.02

Source: Weaver et al. 2019 and Frost & Sullivan analysis

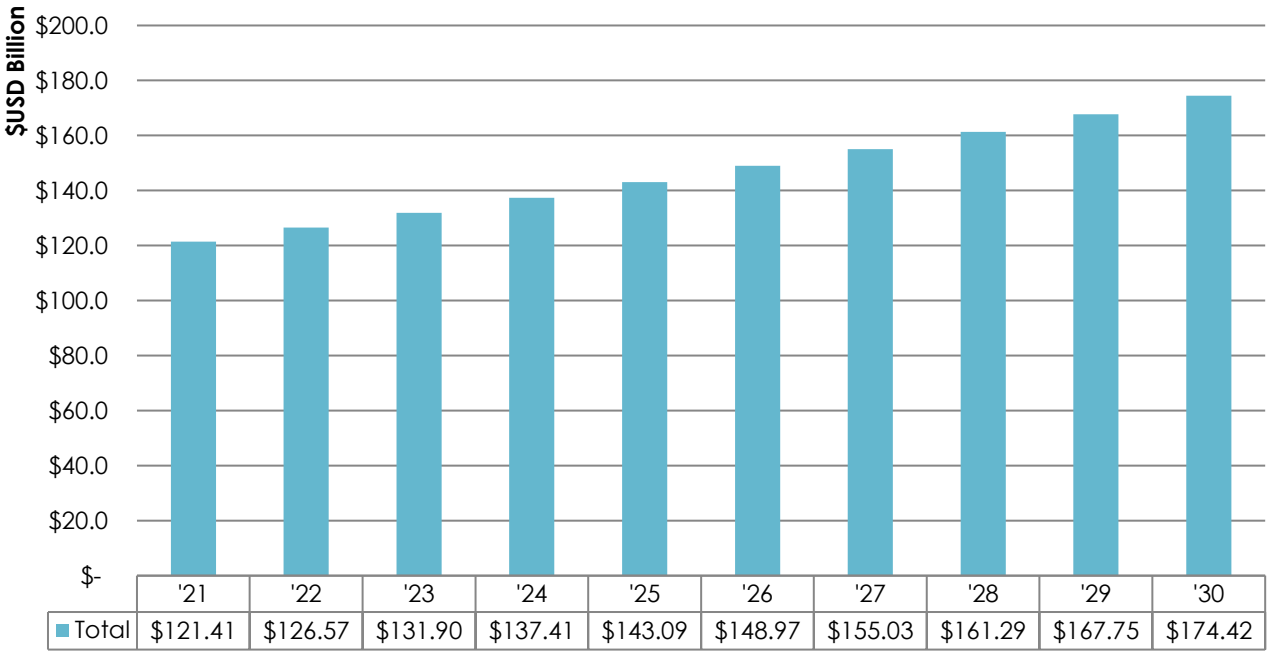
Table 35. Average Health Care Costs and Productivity Losses per Osteoporosis Event, Thousand $USD per Event, United States, 2020-2030

Year	Osteoporosis, Direct Medical Costs ($ per Event Case)	Osteoporosis, Indirect Medical, Pharma, and Productivity Losses ($ per Event Case)	Osteoporosis, Cost per Event Case ($ per Event Case)	Osteoporosis, Total Cost ($ billion)
2021	$15,296	$36,364	$51,660	$121.41
2022	$15,637	$37,176	$52,813	$126.57
2023	$15,986	$38,006	$53,992	$131.90
2024	$16,343	$38,855	$55,198	$137.41
2025	$16,708	$39,722	$56,430	$143.09
2026	$17,081	$40,609	$57,690	$148.97
2027	$17,462	$41,516	$58,978	$155.03
2028	$17,852	$42,442	$60,294	$161.29
2029	$18,250	$43,390	$61,640	$167.75
2030	$18,658	$44,358	$63,016	$174.42
Average ('22-'30)	$17,109	$40,675	$57,784	$149.60
CAGR	2.2%	2.2%	2.2%	4.1%
Cumulative ('22-'30)				$1,346.43

Source: Weaver et al. 2019, US Census, and Frost & Sullivan analysis

After application of this method, it was found that the expected total direct hospital costs of treating a spinal fracture was $15,296 [44,45,46]. Expected indirect costs of post-fracture disability and lost productivity amounted to an additional $36,364 per year [44,45,46]. This equates to a mean per person expenditure of $51,660 in 2021 of which over 30% is attributed to direct medical costs and nearly 70% attributed to indirect medical costs. Therefore, it is expected that the total expected medical expenditures on all osteoporotic fractures for all U.S. adults aged 50 will exceed $174.4 billion by 2030 given an expected compound annual population growth rate of 2.0% and an average rate of inflation rate of 2.7% during the forecast period of 2022 to 2030.

Chart 15. Total Population Health Care Losses and Productivity Losses Attributed to Osteoporosis, $USD Billion, United States, 2020-2030



	'21	'22	'23	'24	'25	'26	'27	'28	'29	'30
Total	$121.41	$126.57	$131.90	$137.41	$143.09	$148.97	$155.03	$161.29	$167.75	$174.42

Source: Weaver et al. 2019, US Census, and Frost & Sullivan analysis

One way to control the burden of growing costs of osteoporosis is to minimize the number of costly osteoporotic fractures that are possible in a target at-risk population. Accordingly, adopting new regimens or routines that have been shown to help to minimize osteoporotic fractures that a person might experience and pay for ought to be considered. The daily use of calcium & vitamin D supplements is one tool that people with osteoporosis can employ to help to gain and realize these obtainable benefits. Specifically, the objective of this case study is to demonstrate that the use of calcium & vitamin D dietary supplement products which have been shown to have positive effects on reducing the risk of fracture will in turn result in positive economic benefits in terms of avoided medical costs.

Table 36. Osteoporosis Cost Summary Statistics for All U.S. Adults aged 50 and over, 2021–2030

Metric	'21	CAGR ('21 - '30)	Average ('22 - '30)
Total population, million people	121.35 M	1.48%	130.86 M
Population with Osteoporosis (people at high risk of experiencing an event), million people	9.03 M	1.75%	9.88 M
Number of Osteoporotic fracture cases, million cases	2.35	1.83%	2.58
Event rate—percent of fracture cases among osteoporotic population, %	26.0%	0.08%	26.1%
Direct cost of Osteoporosis, medical service utilization, $USD per Case	$15,296	2.23%	$17,109
Direct cost of Osteoporosis, pharmaceutical utilization, $USD per Case	$36,364	2.23%	$40,675
Total cost of Osteoporosis, $USD per Case	$51,660	2.23%	$57,784
Total target population cost of Osteoporosis, $USD billion	$121.35 B	1.48%	$130.86 B
Price inflation rate, %	6.95%	--	2.23%

Source: Kanis 2012, Wright et al. 2014, Weaver et al. 2019, US Census, and Frost & Sullivan analysis

Calcium and Vitamin D

Literature Review

Calcium is an essential mineral that plays a vital role in human physiology. Calcium can be obtained naturally through the diet by eating dairy products, such as milk, yoghurt, ice cream and cheese [10]. It is also found in seafood and many plant-based products. Lower amounts of calcium are found in leafy greens, legumes, and nuts [10]. Vitamin D is a fat-soluble vitamin that aids in the absorption of calcium, helps to build overall bone mass, and supports muscles, nerves, and the immune system [10]. The body can produce vitamin D endogenously with exposure to the sun's ultraviolet (UVB) rays. However, most Americans do not naturally produce enough vitamin D through sun exposure to maintain sufficient blood levels of vitamin D [47]. Dietary sources of vitamin D include egg yolks, and fish as well as fortified foods such as milk and cereals [10].

Calcium is an essential mineral for human body to build and maintain bone structure as well as teeth. Calcium is the key to maintain structure and hardness of these body parts. Its absorption and metabolism depend, in part, on vitamin D, and is converted in the kidneys to the biologically active form calcitriol. If an individual is not getting sufficient amounts of calcium and vitamin D, then a decrease in overall bone mass can occur and thus the bones become more brittle and easier to break. There has been a significant amount of research exploring the benefits of calcium and vitamin D utilization among the elderly, where most of the research has focused on the correlation between calcium and vitamin D use and the risk of an osteoporotic bone fracture. Under the regulation of 21 CFR 101.72, the U.S Food & Drug Administration has permitted the use of qualified health claims for calcium & vitamin D for reduced risk of osteoporosis since 2008 [205]. In order to quantify the possible effects of calcium and vitamin D supplementation in the elderly on the risk of osteoporotic fractures, a search for recent meta-analytical studies on this topic was conducted. In 2010, EFSA evaluated the scientific evidence for vitamin D and calcium in osteoporotic fractures and concluded that a cause-effect-relationship had been found [49]. In 2014, Shanahan and de Lorimier conducted a search of the scientific literature that focused on published studies quantifying the effect of utilization on fracture risk in Australia [50]. Forty nine studies from all parts of the world and 7 RCT studies were identified as being eligible of the literature and it was found that the relative risk reduction of an osteoporosis-attributed fracture event given the use of 1,000 mg/day of calcium and 20 µg/day of vitamin D was a statistically significant 19.7% (95% CI: 21.1% to 18.3%) after controlling for variance because of sample size, research methodologies and study protocols, and patient population differences within each study and among all studies [50].

In 2015 and 2016, researchers from the International Osteoporosis Foundation and National Osteoporosis Foundation [51,52] conducted a more recent meta-analysis of the body of literature that tested the hypothesis between calcium and vitamin D supplement intake and the risk of a bone

fracture [51,52]. The authors first conducted a search for all randomized controlled trials (RCTs) that reported a measured effect of calcium plus vitamin D supplementation on fracture incidence. In all, 8 studies including 26,000 subjects met their criteria for inclusion in their primary meta-analysis and included over 1,700 total fractures [51,52]. The final analysis reported a summary relative risk estimate of 0.86 (95% CI: 0.75–0.98), indicating that supplementation would reduce the overall population risk of osteoporotic fracture by 14%. Thus, this current analysis utilized a relative risk reduction (RRR) for total fracture of 0.14 with calcium and vitamin D supplementation. Table 37 shows the descriptive statistics used to derive the economic implications of using calcium & vitamin D dietary supplements to support bone health.

Table 37. Expected Efficacy of Calcium & Vitamin D Supplement on CAD-attributed Event Occurrence

Metric	Measure
Relative risk (weighted for intra-study variance) (RR)	0.86 (95% CI: 0.75-0.98)
Relative risk reduction (weighted for intra-study variance) (RRR)	14.0% (95% CI: 2.0%-25.0%)
Absolute risk reduction (ARR)	3.6% (95% CI: 0.5%-6.5%)
Number of people needed to treat to avoid one osteoporotic fracture (NNT), people	27 (95% CI: 15-192)
Estimated number of events that could have been avoided if the entire target population used calcium & vitamin D in 2022	335,518
Average number of events avoided annually if the entire target population used calcium & vitamin D, 2022-2030	361,507

Source: Weaver et al. 2016, Weaver et al. 2015 and Frost & Sullivan analysis

Economic Implications

The calculated relative risk reduction of an osteoporotic fracture given the use of calcium & vitamin D dietary supplements at the preventive intake levels was 14.0% 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 9.20 million people aged 50 and over would have experienced an osteoporotic fracture in 2022, or 26.1% of the population diagnosed with osteoporosis, 27 people (95% CI: 15-192) would have needed to use calcium & vitamin D supplements at the daily preventive levels to avoid one osteoporotic fracture. This translates to 335,518 potentially avoidable osteoporotic fractures that could have been saved in 2022 and an average of 361,507 avoided events per year from 2022 to 2030 given current population and disease risk growth expectations.

Subsequently, the expected reduction in expenditures in 2022 attributed to avoided osteoporotic fractures would have been $17.7 billion in 2022 given an estimated average osteoporotic fracture cost of $52,813 per case. Given current population growth, disease risk growth and price inflationary factors, the expected cost savings derived from avoided osteoporotic fractures caused by the use of calcium & vitamin D at daily protective intake levels is $20.9 billion per year in total savings from 2022 to 2030.

The cost of daily supplement use also needs to be accounted for in order to ensure all cost factors are considered. Based on the review of the thirty best-selling retail products currently sold through online sales channels, the median cost of a daily dose of calcium & vitamin D is approximately $0.26 per day. Given this daily cost requirement, the median annual expected cost of calcium & vitamin D dietary supplementation for all U.S. adults aged 50 and over would be $94.13 per person per year or $1.02 billion per year for the total population over the period 2022 to 2030. Table 38 provides a summary of the cost of dietary supplementation with calcium & vitamin D of the entire target population.

Table 38. Calcium & Vitamin D Cost Savings Analysis: Summary Results—Cost of Dietary Supplementation of the Target Population, 2022-2030

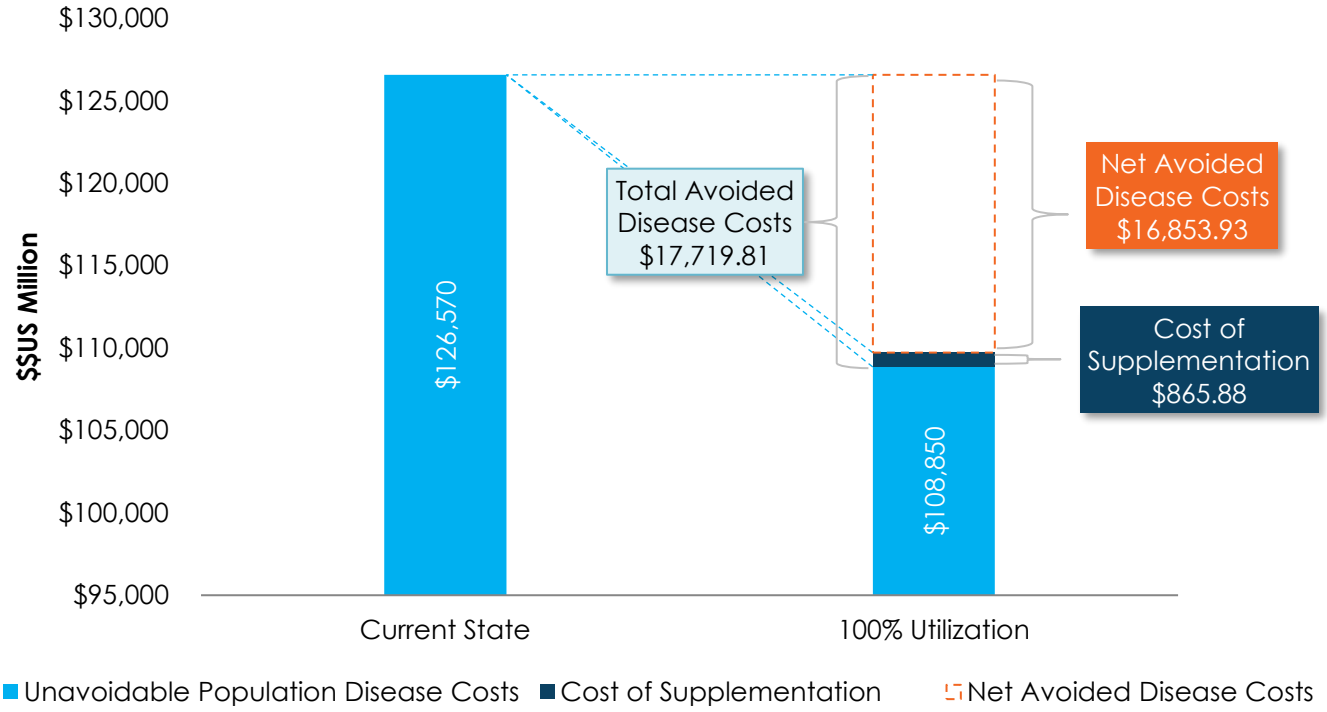
Metric	Measure
Median daily cost per person of Calcium & Vitamin D supplementation at protective daily intake levels, 2022	$0.26
Expected daily median cost per person of Calcium & Vitamin D supplementation at protective daily intake levels, 2022-2030	$0.28
Median annual cost per person of Calcium & Vitamin D supplementation at protective daily intake levels, 2022	$94.13
Expected annual median cost per person of Calcium & Vitamin D supplementation at protective daily intake levels, 2022-2030	$103.05
Total target population cost of Calcium & Vitamin D supplementation at protective daily intake levels, 2022	$0.87 B
Total target population cost of Calcium & Vitamin D supplementation at protective daily intake levels, 2022-2030	$1.02 B

Note: B indicates billion. Source: Frost & Sullivan analysis

After consideration of the cost of calcium & vitamin D dietary supplementation, the net cost savings expected from reduced expenditures in 2022 derived from avoided osteoporotic fractures would have been $16.85 billion in 2022 or $19.92 billion per year in net savings, or $179.32 billion cumulatively, during the period 2022 to 2030.

The above cost saving results are the maximum savings potential that is obtainable if everyone in the target population (all adults aged 50 and older) had not used this product prior to the base year of analysis (e.g., 2022) and then 100% of the population adopted the calcium & vitamin D regimen in the same year and gained all potential benefits. This assumption was made in order to calculate per capita net benefits which in turn can be used to calculate the net avoided cost savings for the subset of the population yet to use calcium & vitamin D.

Chart 16. Calcium & Vitamin D Cost Savings Analysis: Health Care Cost Savings from the Use of Health Supplement, 2022 Scenario Analysis



Note: B indicates billion. Source: Frost & Sullivan analysis

Table 39. Calcium & Vitamin D Cost Savings Analysis: Summary Results—Avoided Hospital Utilization Expenditures due to Dietary Supplement Intervention, 2022-2030

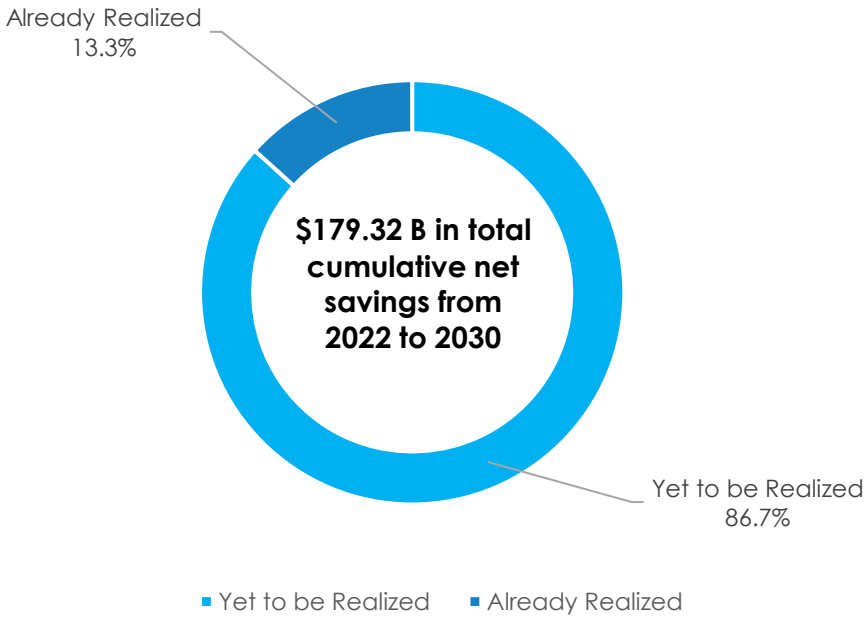
Metric	Measure
Avoided fracture-attributed hospital utilization expenditures given Calcium & Vitamin D supplement intervention per year, 2022	$17.72 B
Average avoided fracture-attributed hospital utilization expenditures given Calcium & Vitamin D supplement intervention per year, 2022-2030	$20.94 B
Net avoided fracture-attributed hospital utilization expenditures given Calcium & Vitamin D supplement intervention per year, 2022 (includes cost of supplementation)	$16.85 B
Net average avoided fracture-attributed hospital utilization expenditures given Calcium & Vitamin D supplement intervention per year, 2022-2030 (includes cost of supplementation)	$19.92 B
Net benefit cost ratio, $ Savings per one dollar spent on dietary supplement	$20.46
Cumulative net target avoided costs, 2022-2030 (NET BENEFITS) ($ billion)	$179.32 B

Note: B indicates billion. Source: Frost & Sullivan analysis

According to the 2021 Council for Responsible Nutrition Consumer Survey on Dietary Supplements conducted by Ipsos Public Affairs, 43% of US adults aged 55 and older are regular users of dietary supplements and approximately 31% of supplement users aged 55 and over are regular users of calcium dietary supplements [152]. It is expected that the calcium products used by these sample of users likely include preventive levels of vitamin D based on formulation standardization across the major manufacturers in the US marketplace. This implies that approximately 13.3% of the total population of US adults aged 55 and older are regular users of calcium & vitamin D dietary supplements and the remaining 86.7% of the target population 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 calcium & 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. It should be noted that the target population of this case study includes individuals younger than 55, so the use of these consumer research findings for deducing the proportion of the population yet to realize the benefits from using this supplement is likely underestimated since use of dietary supplements generally increases with age.

Thus, it is expected that approximately $14.61 billion of the $16.85 billion in net potential direct savings from hospital utilization events related to avoided osteoporotic fractures has yet to be realized. If utilization rates go unchanged, an average cost savings opportunity of $17.27 billion per year, or $155.41 billion from 2022 to 2030 in cumulative savings, could be lost because of underutilization of calcium & vitamin D dietary supplements. Hence it is expected that there are still significant cost savings yet be realized through the increased usage of calcium & vitamin D dietary supplements among the high-risk target population.

Chart 17. Calcium & Vitamin D Cost Savings Analysis: Summary Results—Cumulative Net Cost Savings Yet to be Realized due to Avoided Hospital Utilization Expenditures through Dietary Supplement Intervention, 2022-2030



Source: Council for Responsible Nutrition

Table 40. Calcium & Vitamin D Cost Savings Analysis: Summary Results—Net Cost Savings Yet to be Realized due to Avoided Hospital Utilization Expenditures through Dietary Supplement Intervention, 2022-2030

Metric	Measure
Net avoided fracture-attributed hospital utilization expenditures given Calcium & Vitamin D supplement intervention yet to be realized per year, 2022	$14.61 B
Net average avoided fracture-attributed hospital utilization expenditures given Calcium & Vitamin D supplement intervention yet to be realized per year, 2022-2030	$17.27 B
Cumulative net target avoided costs yet realized, 2022-2030 (NET BENEFITS) ($ billion)	$155.41 B

Note: B indicates billion. Source: Frost & Sullivan analysis

Detailed Results

Table 41. Calcium & Vitamin D Cost Savings Analysis: Detailed Results—Cost of Dietary Supplementation of the Target Population, 2022-2030

Year	Calcium & Vitamin D, Daily Cost of Supplementation ($ per day)	Calcium & Vitamin D, Annual Cost of Supplementation ($ per year)	Calcium & Vitamin D, Population Cost of Supplementation ($ billion)
2021	$0.25	$91.09	$0.822
2022	$0.26	$94.13	$0.866
2023	$0.26	$96.23	$0.902
2024	$0.27	$98.65	$0.941
2025	$0.28	$100.58	$0.976
2026	$0.28	$102.82	$1.015
2027	$0.29	$105.12	$1.056
2028	$0.29	$107.76	$1.101
2029	$0.30	$109.86	$1.141
2030	$0.31	$112.32	$1.185
Average ('22-'30)	$0.28	$103.05	$1.020
CAGR	2.4%	2.4%	4.1%
Cumulative ('22-'30)			$23.240

Source: Frost & Sullivan.

Table 42. Calcium & Vitamin D Cost Savings Analysis: Detailed Results—Avoided Hospital Utilization Expenditures due to Dietary Supplement Intervention, 2022-2030

Year	Calcium & Vitamin D & Osteoporosis, Number of Avoided Events if 100% Utilization by Target User Base (# of Avoided Event Cases)	Calcium & Vitamin D & Osteoporosis, Total Target Avoided Costs (BENEFITS) ($ billion)	Calcium & Vitamin D & Osteoporosis, Net Target Avoided Costs (NET BENEFITS) ($ billion)	Calcium & Vitamin D, Benefit/Cost Ratio: $Value of Reduced Risk per $1 spent on Supplement ($/$1 supplement spend)
2021	329,021	$17.00	$16.17	$20.67
2022	335,518	$17.72	$16.85	$20.46
2023	342,015	$18.47	$17.56	$20.48
2024	348,513	$19.24	$18.30	$20.45
2025	355,010	$20.03	$19.06	$20.52
2026	361,507	$20.86	$19.84	$20.54
2027	368,005	$21.70	$20.65	$20.55
2028	374,502	$22.58	$21.48	$20.51
2029	381,000	$23.48	$22.34	$20.59
2030	387,497	$24.42	$23.23	$20.60
Average ('22-'30)	361,507	$20.94	$19.92	$20.52
CAGR	1.83%	4.11%	4.11%	-0.04%
Cumulative ('22-'30)	3,253,567	$188.500	$179.317	

Source: Frost & Sullivan.

Table 43. Calcium & Vitamin D Cost Savings Analysis: Detailed Results—Net Cost Savings Yet to be Realized due to Avoided Hospital Utilization Expenditures through Dietary Supplement Intervention, 2022-2030

Year	Calcium & Vitamin D & Osteoporosis, Total Target Avoided Costs Yet to be Realized (BENEFITS) ($ billion)	Calcium & Vitamin D & Osteoporosis, Net Target Avoided Costs Yet to be Realized (NET BENEFITS) ($ billion)
2021	$14.73	$14.02
2022	$15.36	$14.61
2023	$16.00	$15.22
2024	$16.67	$15.86
2025	$17.36	$16.52
2026	$18.08	$17.20
2027	$18.81	$17.90
2028	$19.57	$18.62
2029	$20.35	$19.37
2030	$21.16	$20.14
Average ('22-'30)	$18.15	$17.27
CAGR	4.11%	4.11%
Cumulative ('22-'30)	$163.37	$155.41

Source: Frost & Sullivan.

THE ECONOMIC BENEFITS OF USING LUTEIN & ZEAXANTHIN TO SLOW AGE-RELATED MACULAR DEGENERATION

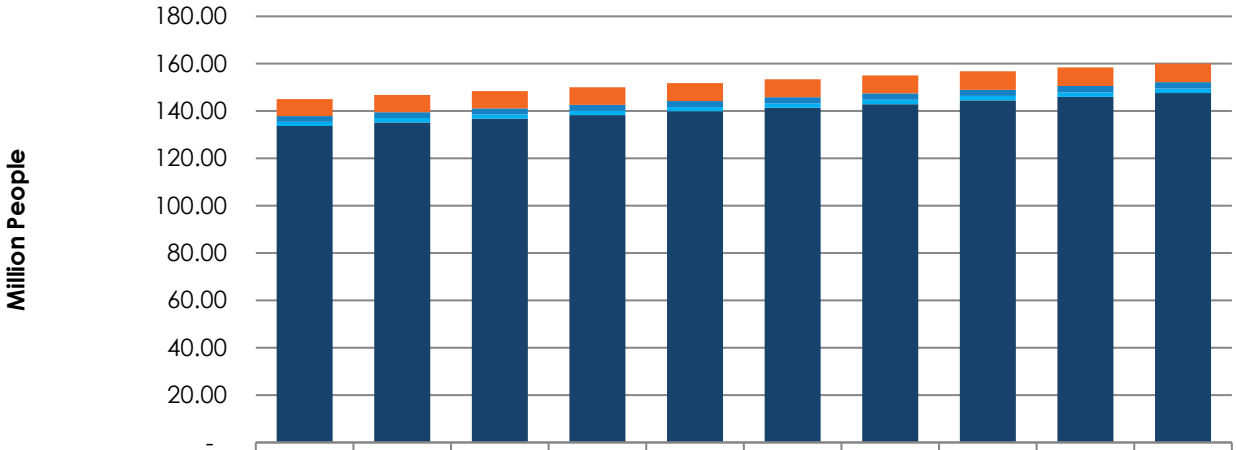
The Burden and Social Consequences

Age-related macular degeneration (AMD) is a progressive degenerative eye disease mostly inflicting many people over the age of 50. AMD is characterized by the degeneration of the central part of the retina known as the macula [53, 54]. AMD is diagnosed by comprehensive eye examination to obtain images of the retina which enable to detect the presence, number, and dimension of drusen (yellow deposits beneath the retina that represent the hallmark of AMD), and the eventual presence of newly formed and/or leaking blood vessels. AMD, which inhibits the ability to see objects directly ahead, can cause irreversible and progressive decline in an individual's independence and ability to perform daily activities, which often leads to significant emotional distress and significantly impacts quality of life [54].

According to the CDC, more than 4.2 million people aged 40 and older suffer from low vision or blindness in 2021, an event risk of 2.9**%** given a total population of 145.10 million Americans aged 44 and older in 2021 [154, 56]. In addition, 7.17 million U.S. adults aged 44 and older had a large drusen and thus are at significant risk of developing AMD in the near future, a risk of transition of 24.7% [8]. Furthermore, 1.78 million U.S. adults aged 44 and older suffer from AMD, an event risk of 1.2% [8]. Among those with AMD, sufferers typically suffer from a significant reduction in visual acuity (VA) or severe vision loss, which causes difficulty in daily activities, some emotional impact and some difficulty going outside the home without assistance and thus requiring long-term care.

Macular pigment optical density, or MPOD, is the quantitative measure of the amount of pigment in each eye's macula and it is expected to be a biomarker of interest in diagnosing and tracking AMD. The pigments, which are carotenoid-based and naturally include both lutein and zeaxanthin, are necessary for optimal optical performance. Macular pigments help to absorb harmful blue light that enters the eye and in turn could cause damage to the eye's photoreceptors [57]. In addition, the concentration of macular pigments in the eye has been tied to visual performance overall in terms of visual acuity, contrast and light sensitivity, and glare recovery caused by high intensity lighting that can cause sunspots and temporary visual impairment [57].

Chart 18. Target Population Size and Prevalence of Low Vision and Blindness, United States, Age 44 and older, 2020-2030



	'21	'22	'23	'24	'25	'26	'27	'28	'29	'30
With Large Drusen	7.23	7.30	7.37	7.44	7.51	7.58	7.65	7.72	7.79	7.86
Other Cause LVB	2.43	2.46	2.49	2.52	2.55	2.58	2.61	2.64	2.67	2.70
Diagnosed AMD	1.78	1.80	1.82	1.83	1.85	1.87	1.89	1.90	1.92	1.94
Healthy Vision	133.67	135.21	136.76	138.30	139.85	141.39	142.94	144.48	146.02	147.57
All Adults	145.10	146.77	148.43	150.09	151.76	153.42	155.08	156.75	158.41	160.07

Source: Centers for Disease Control and Prevention, US Census, and Frost & Sullivan analysis

Table 44. Target Population Size and Prevalence of Low Vision and Blindness, United States, Age 44 and older, 2020-2030

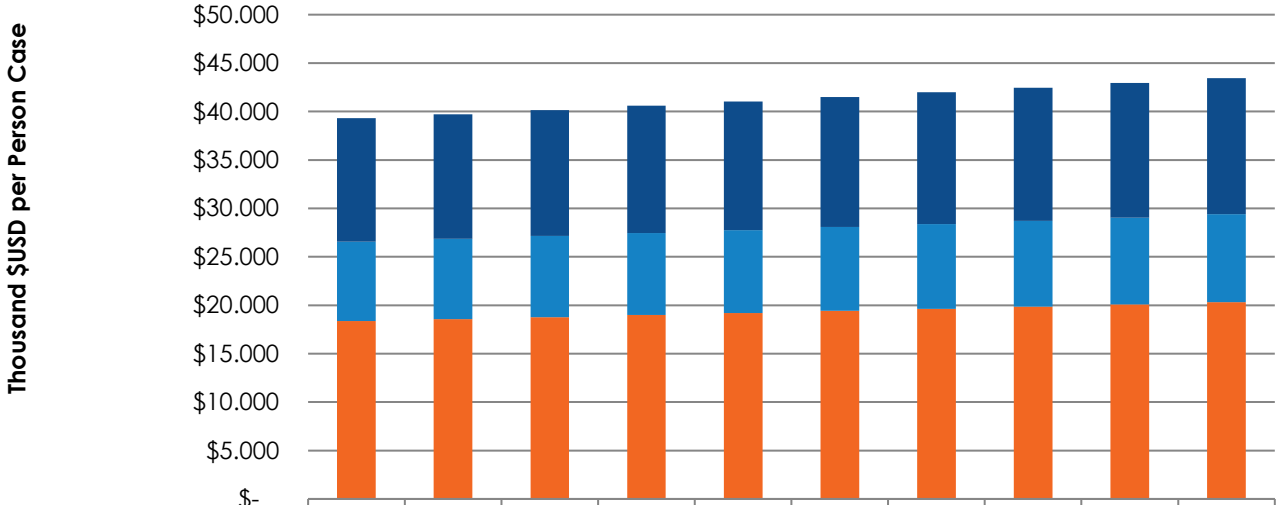
Year	Total Population, age 44 and older (million people)	Population, Diagnosed with Age-Related Macular Degeneration (million people)	Population, Diagnosed with Large Drusen (million people)	Population, Other Low Vision & Blind (million people)	Population, Healthy Vision (million people)
2021	145.10	1.78	7.23	2.43	133.67
2022	146.77	1.80	7.30	2.46	135.21
2023	148.43	1.82	7.37	2.49	136.76
2024	150.09	1.83	7.44	2.52	138.30
2025	151.76	1.85	7.51	2.55	139.85
2026	153.42	1.87	7.58	2.58	141.39
2027	155.08	1.89	7.65	2.61	142.94
2028	156.75	1.90	7.72	2.64	144.48
2029	158.41	1.92	7.79	2.67	146.02
2030	160.07	1.94	7.86	2.70	147.57
Average ('22-'30)	153.42	1.87	7.58	2.58	141.39
CAGR	1.1%	0.9%	0.9%	1.2%	1.1%

Source: Centers for Disease Control and Prevention, US Census, and Frost & Sullivan analysis

Visual acuity is nearly always assessed to verify how the AMD affects visual function and progression [59]. Visual acuity is measured on many scales such as Snellen, LogMAR, and Best Corrected Visual Acuity (BCVA). A common scale used by clinical researchers is the LogMAR which is an acronym that stands for "Logarithm of the Minimum Angle of Resolution" [58]. The range of the LogMAR is typically between "0" for near-perfect vision and 1.4 (or greater) for complete blindness in both eyes [58]. The LogMAR baseline for poorly corrected severe vision impairment is 0.6 or 6/24 vision which is characterized by some vision problems that make it difficult to recognize faces or objects across a room and a LogMAR baseline score of 1.0 is considered legally blind [58,60].

The relationship between MPOD levels and a change in visual acuity has been independently assessed by a number of researchers [61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88]. Puell MC et al. 2013 and Loughman et al. 2010 found that there is a statistically significant positive relationship between a change in MPOD and change in visual acuity [61, 62]. The expected change in population LogMAR given a change in average population MPOD levels from use of lutein & zeaxanthin is 0.026 LogMAR points [61, 62]. Note that the LogMAR score is inversely related to visual acuity; it is expected that given a positive 0.1 change in MPOD levels (measured in optical density units), LogMAR levels decrease by 0.03 basis points less than the placebo group [61, 62].

Chart 19. Average Healthcare Costs per Person with Low Vision and Blindness, Thousand $USD per case, United States, 2020-2030



	'21	'22	'23	'24	'25	'26	'27	'28	'29	'30
Productivity Losses	$12.7	$12.9	$13.0	$13.1	$13.3	$13.4	$13.6	$13.7	$13.9	$14.1
Disease Management	$8.2	$8.3	$8.4	$8.5	$8.6	$8.7	$8.8	$8.9	$9.0	$9.1
Medical	$18.4	$18.6	$18.8	$19.0	$19.2	$19.4	$19.6	$19.9	$20.1	$20.3
Total	$39.3	$39.7	$40.2	$40.6	$41.0	$41.5	$42.0	$42.5	$43.0	$43.5

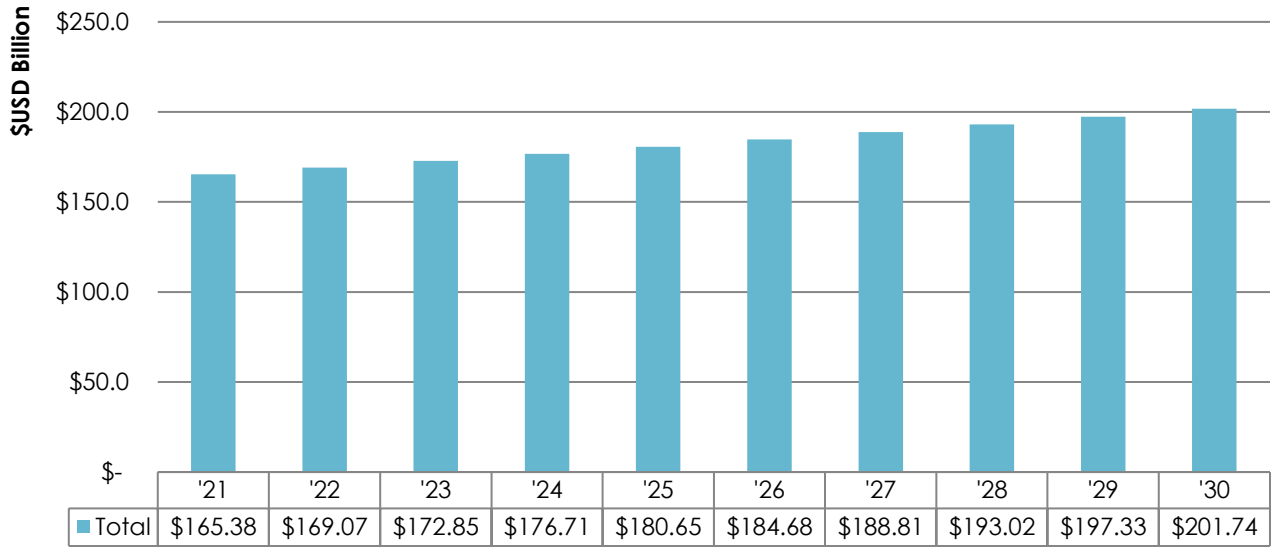
Source: Wittenborn et al 2013 and Frost & Sullivan analysis

Table 45. Healthcare Costs per Person with Low Vision and Blindness, Thousand $USD per case, United States, 2020-2030

Year	Low Vision & Blind, Direct Medical Costs ($ per Event Case)	Low Vision & Blind, Indirect Medical Costs ($ per Event Case)	Low Vision & Blind, Productivity Losses ($ per Event Case)	Low Vision & Blind, Cost per Event Case ($ per Event Case)	Low Vision & Blind, Total Cost ($ billion)
2021	$18,378	$8,199	$12,723	$39,301	$165.4
2022	$18,576	$8,288	$12,860	$39,723	$169.1
2023	$18,777	$8,378	$13,000	$40,155	$172.8
2024	$18,984	$8,470	$13,143	$40,596	$176.7
2025	$19,195	$8,564	$13,289	$41,048	$180.7
2026	$19,411	$8,660	$13,438	$41,509	$184.7
2027	$19,631	$8,759	$13,591	$41,981	$188.8
2028	$19,857	$8,859	$13,747	$42,463	$193.0
2029	$20,087	$8,962	$13,906	$42,955	$197.3
2030	$20,322	$9,067	$14,069	$43,458	$201.7
Average ('22-'30)	$19,427	$8,667	$13,449	$41,543	$185.0
CAGR	1.1%	1.1%	1.1%	1.1%	2.2%
Cumulative ('22-'30)					$1,664.8

Source: Wittenborn et al 2013 and Frost & Sullivan analysis

Chart 20. Total Population Healthcare Costs Attributed to Age-related Macular Degeneration, $USD Billion, United States, 2020-2030



Source: Wittenborn et al 2013, US Census and Frost & Sullivan analysis

Measuring the economic burden of low vision and blindness due to age-related macular degeneration bore by Americans includes a mix of both direct medical costs and indirect non-medical costs related to supporting the individual sufferer's quality of life. According to research by NORC at the University of Chicago, the total cost of vision loss and blindness in the US was $139 billion in 2013 of which $65 billion was attributed to direct medical costs and the remaining $74 billion indirect costs attributed disease burden management and loss productivity [89]. At the time, there were 3.8 million Americas suffering from low vision and blindness at 2013 [89]. Projecting this figure to today given recent trends in prices and population growth, it is expected that the per capita cost of managing the burden of low vision and blindness in the US was $39,310 per person in 2021. The total cost of AMD and other ARED-attributed low vision and blindness in 2021 was $165.4 billion in 2021. Table 46 provides a detailed description of the total and per case medical costs of low vision and blindness due to age-related macular degeneration in the United States.

Lutein and zeaxanthin are xanthophylls, carotenoids that are typically found in the human diet and are well known for their antioxidant properties. Also, lutein and zeaxanthin concentrate in the macula lutea, where they are a key component of the macular pigment, which suggests their important role in protecting eyes and eyesight [90, 10, and 91]. Specifically, recent evidence has found that 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 [90, 10, and 91]. This case study explores the possible health effect and economic benefit that could be expected from the daily use of dietary supplements with effective levels of lutein and zeaxanthin intake to inhibit the rate of visual acuity decline typically associated with age-related macular degeneration. This will be done by determining the potential cost savings that could be realized given the usage of lutein and zeaxanthin dietary supplements that are scientifically shown to reduce the occurrence of age-related visual acuity decline episodes among adults aged 44 and older. Specifically, this report will attempt to show that using lutein & zeaxanthin dietary supplements by subjects with low vision and blindness due to age-related macular degeneration can result in health care-related cost savings.

Table 46. Age-related Low Vision and Blindness Demographic Descriptive Statistics for All U.S. Adults Aged 44 and over, 2021–2030

Metric	'21	CAGR ('21 - '30)	Average ('22 - '30)
Total population, age 44 and older, million people	145.10 M	1.1%	153.42 M
Population with Age-Related Macular Degeneration (AMD), million people	1.78 M	0.9%	1.87 M
Population with Other Cause Low Vision and Blindness, million people	2.43 M	1.2%	2.58 M
Population with Large Drusen, million people	7.23 M	0.9%	7.58 M
Estimated LogMAR of individuals with Age-Related Macular Degeneration (AMD), Score	--	--	1.00
Estimated LogMAR of individuals with Other Cause Low Vision and Blindness, Score	--	--	0.67
Estimated LogMAR of individuals with Large Drusen, Score	--	--	0.33
Estimated LogMAR of individuals Healthy Vision, Score	--	--	0.00
Direct cost of Age-related Macular Degeneration, medical service utilization, $USD per Case	$18,378	1.1%	$19,427
Direct cost of Age-related Macular Degeneration, pharmaceutical utilization, $USD per Case	$8,199	1.1%	$8,667
Indirect cost of Age-related Macular Degeneration, disease management, $USD per Case	$12,723	1.1%	$13,449
Total cost of Age-related Macular Degeneration, $USD per Case	$39,301	1.1%	$41,543
Total target population cost of Age-related Macular Degeneration and ARED-attributed Low Vision and Blindness, $USD billion	$165.4	2.2%	$185.0
Price inflation rate, %	6.95%	--	2.23%

Source: Centers for Disease Control and Prevention, Wittenborn et al 2013, US Census and Frost & Sullivan analysis

Lutein & Zeaxanthin

Literature Review

Lutein and zeaxanthin are xanthophyllic carotenoids that are typically found in the human diet [10]. Rich sources of lutein and zeaxanthin are green vegetables, particularly dark green leafy vegetables such as spinach and kale, orange pepper, maize, and eggs [10]. Lutein and zeaxanthin are well known for their antioxidant properties that help protect cells against damage caused by dangerous, naturally occurring chemicals known as free radicals. Also, lutein and zeaxanthin are selectively concentrated in the macula lutea, where they are a key component of the macular pigment, which suggests their important role in protecting eyes and eyesight [10, 90]. Like all the carotenoids, lutein and zeaxanthin are not synthesized by the body; these nutrients must be consumed from the diet from lutein and zeaxanthin rich foods or through food supplementation [10].

The American Optometric Association (AOA) proposes that 10 mg per day of lutein and 2 mg per day of zeaxanthin benefits eye health based on results of recent clinical research [91]. This recommended dose, which is based on the observations from the US National Eye Institute sponsored Age-Related Eye Disease Study II (AREDS2), is assumed to be sufficient to derive the expected benefits and is also the quantity found in the majority of products currently in the market today [92,93].

Recent studies have revealed that increasing intake with lutein and/or zeaxanthin in AMD patients leads to an increase in macular pigment and improved visual acuity. For example, Liu et al. (2014) conducted a detailed meta-analysis of eight randomized controlled trials (RCTs) of AMD patients (n=1,176 patients) that explored the relationship between lutein and zeaxanthin intake and its effect on visual acuity [94]. The researchers found that the groups of users with mild AMD using 10 to 20 mg of lutein and/or 0.6 to 10 mg of zeaxanthin – the typical amount in the AREDS2 formulation which also includes vitamin E, copper, and zinc – versus users of a placebo had a baseline LogMAR levels of VA by a statistically significant 0.04 basis point less than the placebo group. This implies that there were significantly less transitions from mild to severe cases of AMD in the lutein & zeaxanthin groups compared to the placebo group [56].

In 2013, Frost & Sullivan conducted a similar assessment of the use of lutein & zeaxanthin on the incidence of both age-related macular degeneration and cataracts. In this case study, the analysis has been modified by specifically looking at how use of lutein & zeaxanthin supplements impacts MPOD levels which in turn impacts visual acuity and risk of age-related eye disorders.

Specifically, there are over 20 years of scientific publications indicating that higher lutein and zeaxanthin intake is associated with higher macular pigment optical density (MPOD). Based on a rigorous systematic review of the scientific literature, 59 studies were identified in a search exercise

(see research methodology) based on using key words related to use of lutein and zeaxanthin and a number of biomarkers that are typically used as proxies for measuring relative eye health, including "MPOD" and "visual acuity". Of this set of studies, 24 clinical studies were identified that tested the same hypothesis that use of lutein and zeaxanthin resulted in a change in MPOD levels between an observed treatment group and a placebo group. The objective of this meta-analysis was to identify the best set of studies that tested using similar study protocols for a direct causal relationship between intake of lutein and zeaxanthin and the MPOD levels. Studies were not selected on the basis of the magnitude, direction, or statistical significance of the reported findings. Table 47 provides a description of a selection of included studies in the final meta-analysis described below.

From this qualified set, the studies' findings were weighted using a random-effects meta-analysis process by sample size and inter-study variance and aggregated to determine an overall expected effect size of a lutein & zeaxanthin supplement intervention on relative MPOD levels [69]. Among the 24 qualified studies, the dose size ranges were 5 to 20 mg of lutein and 0 to 20 mg of zeaxanthin. The typical dose size was 10 mg of lutein and 2 mg of zeaxanthin. See Table 48 for the results of the meta-analysis.

Based on the results of the random-effects meta-analysis, the expected change in macular pigment optical density (MPOD) among users of lutein and zeaxanthin daily at supportive intake levels was a positive 0.088 optical density unit increase compared to the control group using a placebo. This expected 0.088 optical density unit increase is controls for both intra-study and inter-study variance through weights derived from relative study sample size and reported confidence intervals of each study's findings.

Table 47. Lutein & Zeaxanthin Literature Review: Description of the Qualified Studies

Ref.	Studies	Year	Dose Size of Lutein	Dose Size of Zeaxanthin	Sample Size	Disease State of Patient Population
95	Wilson L. et al.	2021	5 to 20 mg per day		215	Healthy Eyes and AMD
96	Arnold C et al.	2013	10	3	20	AMD
97	Bone, R.A et al.	2007	5.5	1.4	19	Healthy Eyes
98	Bone, R.A et al.	2010	5	20	100	Healthy Eyes
99	Bovier, E.R et al.	2015	8	20	102	Healthy Eyes
100	Connolly, E.E et al..	2011	5.9	1.2	44	Healthy Eyes
101	Curran-Celentano J et al.	2001	0.28 ± 0.13 micro mol/L	0.091 ± 0.044 micro mol/L	280	AMD
102	Dawczynski, J et al.	2013	10	1	172	AMD
103	García-Layana, A et al.	2013	12	0.6	44	AMD
104	Huang, Y.M et al.	2015	12.5	10	112	AMD
105	Johnson, E.J et al.	2008	12	0.5	57	Healthy Eyes
106	Kvansakul, J. et al.	2006	10	10	92	Healthy Eyes
107	Landrum, J et al.	2012	20	0	30	Healthy Eyes
108	Loughman, J et al.	2012	20	2	36	Healthy Eyes
109	Murray, I.J et al..	2013	10	0	72	AMD
110	Nolan JM et al.	2007	[A]	[B]	28	AMD
111	Nolan, J.M et al.	2011	12	1	121	Healthy Eyes
112	Nolan, J.M et al.	2016	10	2	105	Healthy Eyes
113	Richer, S et al.	2007	10	0	90	AMD
114	Trieschmann et al.	2007	12	2	130	AMD
115	van der Made SM et al.	2014	[C]	[C]	101	AMD
116	Weigert, G et al.	2011	15	0	126	AMD
117	Wolf-Schnurrbusch UE et al.	2015	10	1	79	AMD
118	Yao, Y et al.	2013	10	2	120	Healthy Eyes

[A] Entire study group Serum Lutein L (µ g/mL): 0.280 (Absolute Dietary L(mg/day)); 0.303* (Energy-Adjusted Dietary L); 0.299* (Nutrient Density of Dietary L); 1 (Serum L (µ g/mL))

[B] Entire study group Serum zeaxanthin (Z) (µ g/mL) :0.160* (Absolute Dietary L (mg/day)); 0.166* (Energy-Adjusted Dietary L); 0.146* (Nutrient Density of Dietary L); 0.462* (Serum L (µ g/mL)); 0.237* (Absolute Dietary Z (mg/day)); 0.260*(Energy-Adjusted Dietary Z); 0.259* (Nutrient Density of Dietary Z); 1 Serum Z (µ g/mL)

[C] 1-y daily consumption of a buttermilk drink containing 1.5 lutein-rich egg yolks

Table 48. Lutein & Zeaxanthin Literature Review: Systematic Review Results

Ref.	Studies	Weighted Mean Difference (Δ in MPOD)	CI 95% Min	CI 95% Max	Sample Size Weight	Std. VAR Weight	Average Weight
95	Wilson L et al.	0.040	0.020	0.070	9.37%	5.57%	7.47%
96	Arnold C et al.	0.270	0.230	0.310	0.96%	3.71%	2.34%
97	Bone, R.A et al.	0.030	-0.020	0.080	4.81%	2.97%	3.89%
98	Bone, R.A et al.	0.240	0.180	0.300	0.91%	2.47%	1.69%
99	Bovier, E.R et al.	0.110	0.020	0.200	4.90%	1.65%	3.28%
100	Connolly, E.E et al.	0.050	-0.060	0.160	2.12%	1.35%	1.73%
101	Curran-Celentano J et al.	0.210	0.050	0.350	13.46%	0.99%	7.22%
102	Dawczynski, J et al.	0.030	0.030	0.030	8.27%	0.15%	4.21%
103	García-Layana, A et al.	-0.100	-0.110	-0.090	2.12%	14.84%	8.48%
104	Huang, Y.M et al.	0.100	0.040	0.160	5.38%	2.47%	3.93%
105	Johnson, E.J et al.	0.120	-0.130	0.370	2.74%	0.59%	1.67%
106	Kvansakul, J. et al.	0.040	0.040	0.040	4.42%	0.15%	2.29%
107	Landrum, J et al.	0.050	-0.070	0.170	1.44%	1.24%	1.34%
108	Loughman, J et al.	0.060	-0.060	0.180	1.73%	1.24%	1.48%
109	Murray, I.J et al.	0.150	0.060	0.240	3.46%	1.65%	2.55%
110	Nolan JM et al.	0.208	0.136	0.303	1.35%	1.77%	1.56%
111	Nolan, J.M et al.	0.100	0.040	0.160	5.82%	2.47%	4.14%
112	Nolan, J.M et al.	0.120	0.090	0.150	5.05%	4.95%	5.00%
113	Richer, S et al.	0.120	-0.200	0.440	4.33%	0.46%	2.40%
114	Trieschmann et al.	0.070	0.060	0.080	6.25%	14.84%	10.54%
115	van der Made SM et al.	0.070	0.050	0.090	4.86%	7.42%	6.14%
116	Weigert, G et al.	0.080	0.070	0.090	6.06%	14.84%	10.45%
117	Wolf-Schnurrbusch UE et al.	0.120	0.121	0.119	3.80%	14.84%	9.32%
118	Yao, Y et al.	0.110	0.060	0.160	5.77%	2.97%	4.37%

	Weighted Mean Difference (Δ in MPOD)	CI 95% Min	CI 95% Max
Expected WMD - All People	**0.085**	**0.036**	**0.133**

Source: Frost & Sullivan analysis

As previously noted, the relationship between MPOD levels and a change in visual acuity had been independently assessed by a number of researchers including Puell et al. 2013 and Loughman et al. 2010 [61, 62]. Both researchers found that there is a statistically significant positive relationship between a change in MPOD and change in visual acuity. It is expected that given a positive 0.1 change in MPOD levels (measured in optical density units), LogMAR levels decrease by 0.03 basis point less than the placebo group. Because now that it is known that MPOD increases at a weighted average of 0.085 optical density units given the use of lutein zeaxanthin at supportive intake levels from the meta-analysis results, the expected change in population LogMAR given a change in average population MPOD levels from use of lutein & zeaxanthin can be deduced. Specifically, the basis point decrease in LogMAR given the use of lutein & zeaxanthin at supportive intake levels is 0.025 (95% CI: 0.011-0.039). Thus, there would be an increase in average visual acuity levels in the population leading to a lessening of dependency on medical services and other services required to maintain an acceptable quality of life for those inflicted with severe visual impairment or blindness. Note that the 2014 meta-analysis developed by Lui et al. (2014) deduced a 0.04 basis point impact on LogMAR from use of lutein & zeaxanthin, which looked at completely different set of clinical studies that explored the direct relationship between lutein and zeaxanthin use and observed visual acuity levels as opposed to the direct relationship between lutein and zeaxanthin use and MPOD levels explored in this case study [94].

By applying the information of the change in visual acuity given the use of lutein & zeaxanthin to current knowledge on the population prevalence of age-related macular degeneration and low vision people in general, the potential percent change in population prevalence of age-related macular degeneration given the use of lutein and zeaxanthin can be determined. As noted previously, there are 11.6 million Americans aged 44 and older that have some type of vision problem and based on the mix of vision disorder types it is expected that the baseline LogMAR of this target population is 0.574. Subtracting 0.025 LogMAR basis points from baseline LogMAR yields an estimate for the consequential LogMAR score the total target population of low vision Americans would have if 100% of this population had used a lutein & zeaxanthin supplement at daily supportive levels which is 0.549. This is equivalent to a 4.4% improvement in the target population's visual acuity. Assuming that the improvement is shared across the entire target population, we would expect to see up to 21,022 avoided transitions in 2022 to a more severe vision impairment state. The number of potentially avoidable prevalent cases of severe visual acuity decline transition episodes could surpass 22,414 cases in 2030 if all eligible users used lutein & zeaxanthin dietary supplements at daily supportive intake levels. Table 49 provides a description of the calculation steps used to derive the number of potentially avoidable transitions to more severe cases of vision loss and blindness.

Table 49. Steps to Derive Expected Change in Population Prevalence Given a Change in Visual Acuity, 2022

Step	Measure	AMD	Other ARED Low vision or blindness	Large Drusen	Healthy Eyes	Total	Notes
A	Current Population Prevalence, Age 44 and older, million people	1.80	2.46	7.30	135.21	146.77	--
B	% Current Population Prevalence, Age 44 and older, %	1.23%	1.67%	4.97%	92.13%	100.0%	--
C	Current Population Prevalence, % of total Vision Impaired	24.7%	33.6%	41.7%	--	100% of vision impaired population	--
D	LogMAR Baseline Level	1.00	0.60	0.30	0.00	0.574	
E	Reduction in LogMAR given use of lutein and zeaxanthin (from meta-analysis)	--	--	--	--	**-0.0251**	--
F	Updated LogMAR Baseline Level given use of lutein and zeaxanthin	--	--	--	--	0.548	F = D - E
G	% Reduction in LogMAR Levels	--	--	--	--	95.6%	G = F / D
H	Population Prevalence Given use of Lutein & Zeaxanthin, % of total Population	1.1659%	1.5910%	4.7286%	92.5145%	--	H = G x B
I	Implied Absolute Risk Reduction: Difference in Population Prevalence Given use of Lutein & Zeaxanthin, % of total Population	-0.06%	-0.08%	-0.25%	0.39%		*I* = H - B
J	Number of Avoided Transitions to More Severe Vision Impairment, people cases	1,089	2,027	17,906		**21,022**	J = -1*I*A

*Equals 100% minus 4.4% Visual Acuity Improvement. Source: Frost & Sullivan analysis

Economic Implications

As stated above, the expected number of avoided age-related vision loss transition events given the use of lutein & zeaxanthin dietary supplements at preventive intake levels was 21,022 potentially avoidable events in 2022 and an average of 21,718 avoided events per year from 2022 to 2030 given current population and disease risk growth expectations. Subsequently, the expected reduction in health care expenditures in 2022 attributed to avoided age-related vision loss transition events would have been $835.1 million in 2022 given an average age-related macular degeneration transition person case cost of $39,723 per year. Given current population growth, disease risk growth and price inflationary factors, the expected cost savings derived from avoided age-related vision loss transition events caused by the use of lutein & zeaxanthin at daily protective intake levels is $902.8 million per year in total savings from 2022 to 2030.

It is proper to include the cost of using lutein & zeaxanthin supplements daily in the final accounting in order to ensure all cost components are considered. Based on the review of the thirty best-selling retail products currently sold through online sales channels, the median cost of a daily dose of dietary supplements that contains one or more of the lutein & zeaxanthin is approximately $0.27 per day. Given this daily cost requirement, the median annual expected cost of lutein & zeaxanthin dietary supplementation for all U.S. adults aged 44 and over would be $104.96 per person per year or $796.2 million per year for the target population of people diagnosed with a large drusen over the period 2022 to 2030. Table 50 provides a summary of the cost of dietary supplementation with lutein & zeaxanthin of the entire target population.

Table 50. Lutein & Zeaxanthin Cost Savings Analysis: Summary Results—Cost of Dietary Supplementation of the Target Population, 2022-2030

Metric	Measure
Median daily cost per person of Lutein & Zeaxanthin supplementation at protective daily intake levels, 2022	$0.27
Expected daily median cost per person of Lutein & Zeaxanthin supplementation at protective daily intake levels, 2022-2030	$0.29
Median annual cost per person of Lutein & Zeaxanthin supplementation at protective daily intake levels, 2022	$100.30
Expected annual median cost per person of Lutein & Zeaxanthin supplementation at protective daily intake levels, 2022-2030	$104.96
Total target population cost of Lutein & Zeaxanthin supplementation at protective daily intake levels, 2022	$732.2 M
Total target population cost of Lutein & Zeaxanthin supplementation at protective daily intake levels, 2022-2030	$796.2 M

Note: M indicates million. Source: Frost & Sullivan analysis

Based the incurred cost of lutein & zeaxanthin dietary supplementation, the net cost savings expected from reduced health care-attributed expenditures in 2022 derived from avoided age-related vision loss transition events would have been $102.9 million in 2022, or $959.2 million in cumulative net savings during the period 2022 to 2030. Table 51 reports the economic implications of the systematic review finding of the beneficial use of lutein & zeaxanthin supplements to support age-related eye health.

Table 51. Lutein & Zeaxanthin Cost Savings Analysis: Summary Results—Avoided Healthcare Expenditures due to Dietary Supplement Intervention, 2022-2030

Metric	Measure
Avoided Age-related Macular Degeneration-attributed healthcare expenditures given Lutein & Zeaxanthin supplement intervention per year, 2022	$835.1 M
Average avoided Age-related Macular Degeneration-attributed healthcare expenditures given Lutein & Zeaxanthin supplement intervention per year, 2022-2030	$902.8 M
Net avoided Age-related Macular Degeneration-attributed healthcare expenditures given Lutein & Zeaxanthin supplement intervention per year, 2022 (includes cost of supplementation)	$102.9 M
Net average avoided Age-related Macular Degeneration-attributed healthcare expenditures given Lutein & Zeaxanthin supplement intervention per year, 2022-2030 (includes cost of supplementation)	$106.6 M
Net benefit cost ratio, $ Savings per one dollar spent on dietary supplement	$1.13
Cumulative net target avoided costs, 2022-2030 (NET BENEFITS) ($ million)	$959.2 M

Note: M indicates million. Source: Frost & Sullivan analysis

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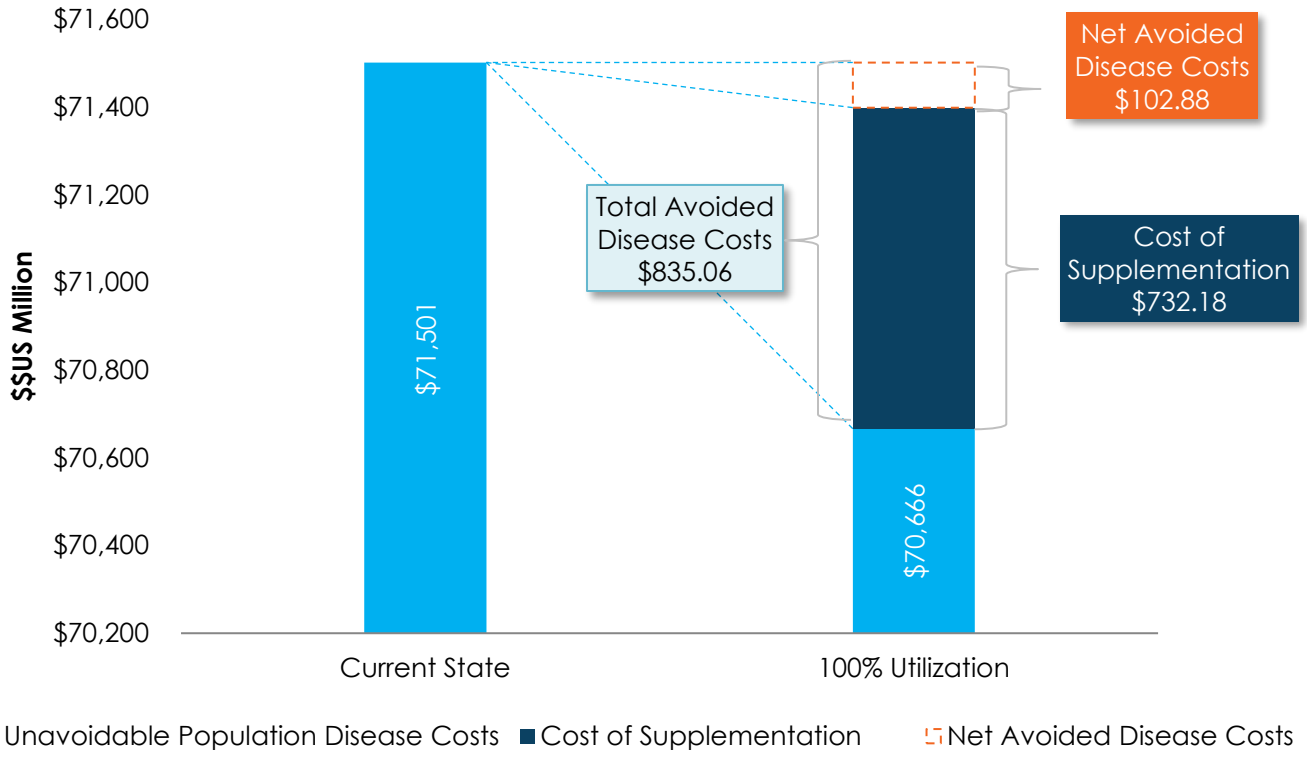
Chart 21. Lutein & Zeaxanthin Cost Savings Analysis: Healthcare Cost Savings from the Use of Health Supplement, 2022 Scenario Analysis



Note: M indicates million. Source: Frost & Sullivan analysis

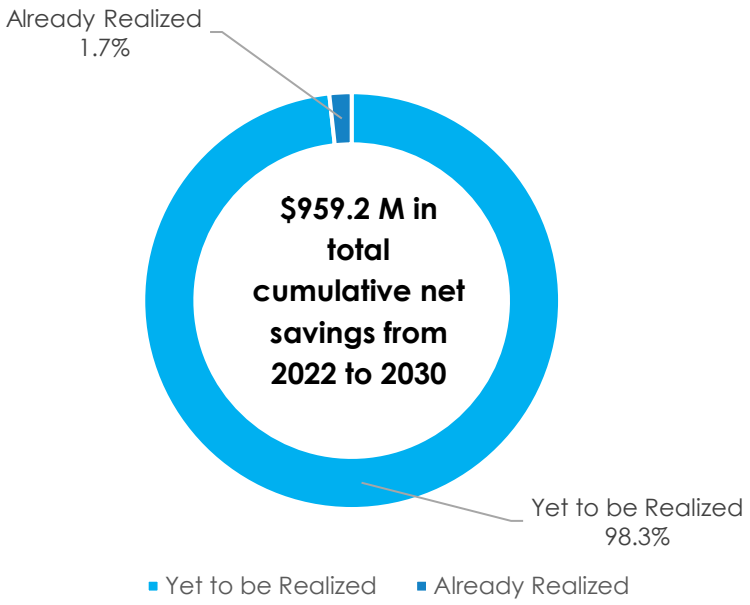
The above cost savings results are the maximum savings potential that is obtainable if everyone in the target population (all adults aged 44 and older) had not used this product prior to the base year of analysis (e.g., 2022) and then 100% of the population adopted the lutein & zeaxanthin regimen in the same year and gained all potential benefits. This assumption was made in order to calculate per capita net benefits which in turn can be used to calculate the net avoided cost savings for the subset of the population yet to use lutein & zeaxanthin.

According to the 2021 Council for Responsible Nutrition Consumer Survey on Dietary Supplements conducted by Ipsos Public Affairs, over 40% of US adults aged 55 and older are regular users of dietary supplements and only 4.0% of supplement users aged 55 and over reported being regular users of lutein dietary supplements, or 1.7% of the total target population [152]. This implies that the remaining 98.3% of the target population has yet to realize the potential benefits of the supplements' regular use on eye health. Because avoided expenditures and net cost savings are a direct function of the total number of people in the target population using lutein & zeaxanthin 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 should be noted that the target population of this case study includes individuals

younger than 55, so the use of these consumer research findings for deducing the proportion of the population yet to realize the benefits from using this supplement is likely underestimated since use of dietary supplements generally increases with age.

Despite this, it is expected that at least $101.1 million of the $102.9 million in net potential direct savings in 2022 from avoided age-related eye health events because of lutein & zeaxanthin dietary supplement intervention was not realized. This corresponds to an average of $104.7 million per year in net savings yet to be realized, or $942.7 million in cumulative savings from 2022 to 2030, due to underutilization of lutein & zeaxanthin dietary supplements. Thus, there are still significant cost savings potential from the increased use of lutein & zeaxanthin dietary supplements among the high-risk target population.

Chart 22. Lutein & Zeaxanthin Cost Savings Analysis: Summary Results—Cumulative Net Cost Savings Yet to be Realized due to Avoided Hospital Utilization Expenditures through Dietary Supplement Intervention, 2022-2030



Source: Council for Responsible Nutrition

Table 52. Lutein & Zeaxanthin Cost Savings Analysis: Summary Results—Net Cost Savings Yet to be Realized due to Avoided Healthcare Expenditures through Dietary Supplement Intervention, 2022-2030

Metric	Measure
Net avoided Age-related Macular Degeneration -attributed healthcare expenditures given Lutein & Zeaxanthin supplement intervention yet to be realized per year, 2022	$101.1 M
Net average avoided Age-Related Macular Degeneration-attributed healthcare expenditures given Lutein & Zeaxanthin supplement intervention yet to be realized per year, 2022-2030	$104.7 M
Cumulative net target avoided costs yet realized, 2022-2030 (NET BENEFITS) ($ million)	$942.7 M

Note: M indicates million. Source: Frost & Sullivan analysis

Detailed Results

Table 53. Lutein & Zeaxanthin Cost Savings Analysis: Detailed Results—Cost of Dietary Supplementation of the Target Population, 2022-2030

Year	Lutein & Zeaxanthin, Daily Cost of Supplementation ($ per day)	Lutein & Zeaxanthin, Annual Cost of Supplementation ($ per year)	Lutein & Zeaxanthin, Population Cost of Supplementation ($ billion)
2021	$0.27	$97.06	$0.702
2022	$0.27	$100.30	$0.732
2023	$0.28	$101.42	$0.747
2024	$0.28	$102.83	$0.765
2025	$0.28	$103.70	$0.779
2026	$0.29	$104.85	$0.795
2027	$0.29	$106.02	$0.811
2028	$0.29	$107.50	$0.830
2029	$0.30	$108.40	$0.845
2030	$0.30	$109.61	$0.862
Average ('22-'30)	$0.29	$104.96	$0.796
CAGR	1.4%	1.4%	2.3%
Cumulative ('22-'30)			$7.166

Source: Frost & Sullivan.

Table 54. Lutein & Zeaxanthin Cost Savings Analysis: Detailed Results—Avoided Healthcare Expenditures due to Dietary Supplement Intervention, 2022-2030

Year	Lutein & Zeaxanthin & Low Vision & Blind, Number of Avoided Transitions to More Severe Vision Impairment (# of Avoided Event Cases)	Lutein & Zeaxanthin & Low Vision & Blind, Total Target Avoided Costs (BENEFITS) ($ billion)	Lutein & Zeaxanthin & Low Vision & Blind, Net Target Avoided Costs (NET BENEFITS) ($ billion)	Lutein & Zeaxanthin, Benefit/Cost Ratio: $Value of Reduced Risk per $1 spent on Supplement ($/$1 supplement spend)
2021	20,849	$0.819	$0.118	$1.17
2022	21,022	$0.835	$0.103	$1.14
2023	21,196	$0.851	$0.104	$1.14
2024	21,369	$0.868	$0.102	$1.13
2025	21,543	$0.884	$0.106	$1.14
2026	21,717	$0.901	$0.107	$1.13
2027	21,891	$0.919	$0.108	$1.13
2028	22,065	$0.937	$0.107	$1.13
2029	22,240	$0.955	$0.111	$1.13
2030	22,414	$0.974	$0.112	$1.13
Average ('22-'30)	21,718	$0.903	$0.107	$1.13
CAGR	0.81%	1.94%	-0.50%	-0.36%
Cumulative ('22-'30)	195,458	$8.125	$0.959	

Source: Frost & Sullivan.

Table 55. Lutein & Zeaxanthin Cost Savings Analysis: Summary Results—Net Cost Savings Yet to be Realized due to Avoided Healthcare Expenditures through Dietary Supplement Intervention, 2022-2030

Year	Lutein & Zeaxanthin & Low Vision & Blind, Total Target Avoided Costs Yet to be Realized (BENEFITS) ($ billion)	Lutein & Zeaxanthin & Low Vision & Blind, Net Target Avoided Costs Yet to be Realized (NET BENEFITS) ($ billion)
2021	$0.805	$0.116
2022	$0.821	$0.101
2023	$0.836	$0.102
2024	$0.853	$0.101
2025	$0.869	$0.104
2026	$0.886	$0.105
2027	$0.903	$0.106
2028	$0.921	$0.105
2029	$0.939	$0.109
2030	$0.957	$0.110
Average ('22-'30)	$0.887	$0.105
CAGR	1.94%	-0.50%
Cumulative ('22-'30)	$7.99	$0.9427

Source: Frost & Sullivan.

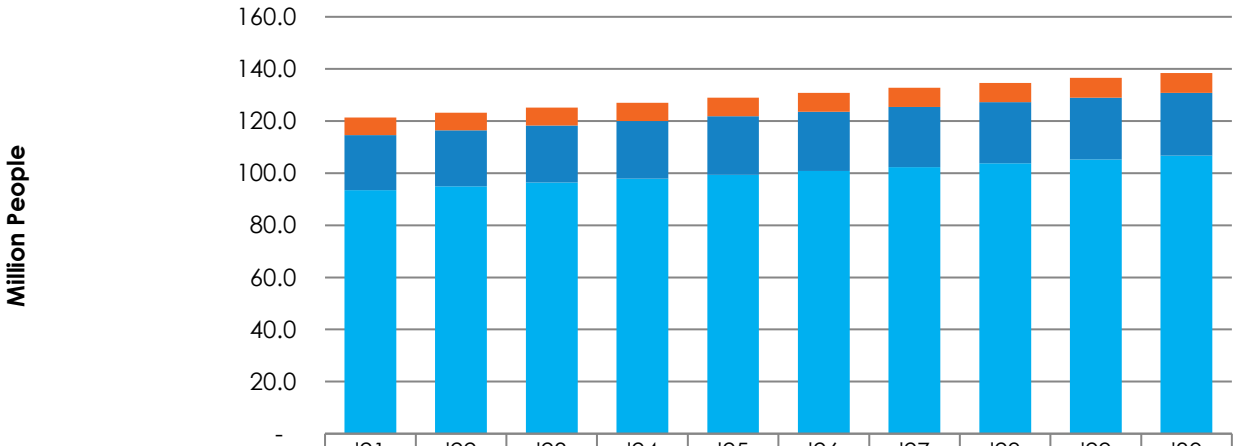
HEALTHCARE COST SAVINGS DERIVED FROM SLOWING COGNITIVE DECLINE WITH THE USE OF B VITAMINS

The Burden and Social Consequences

One critical age-related set of disorders that has had a significant impact on the demand for specialized medical services and long-term professional dependency care is cognitive impairment. Cognitive decline is a normal process that occurs during aging, but certain conditions or diseases are responsible for non-normative cognitive decline and eventual progression to dementia, which also accelerates direct and indirect care costs [119]. There are several distinct diseases that are classified under the umbrella term "dementia" including neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and vascular dementia [120].

It is expected that 21.5 million individuals aged 50 and older suffered from mild cognitive impairment (MCI) in the US in 2022 and an additional 6.78 million Americans have been diagnosed with a dementia disorder (over 5 million of these cases are attributed to Alzheimer's disease alone) where each individual case requires additional medical and non-medical services that goes beyond what is required among those individuals with normal cognitive health [121, 122, 123]. It is estimated that 10% to 15% of individuals with mild cognitive impairment will go on to develop dementia each year [124].

Chart 23. Target Population Size and Prevalence of Mild Cognitive Impairment and Dementia Disorders, United States, Age 50 and older, 2020-2030



	'21	'22	'23	'24	'25	'26	'27	'28	'29	'30
Dementia	6.7	6.8	6.9	7.0	7.1	7.2	7.3	7.4	7.6	7.7
Mild Cognitive Impaired	21.1	21.5	21.8	22.1	22.5	22.8	23.1	23.5	23.8	24.1
Heathy Adults	93.5	95.0	96.4	97.9	99.4	100.8	102.3	103.8	105.2	106.7
All Adults	121.4	123.3	125.2	127.1	129.0	130.9	132.8	134.7	136.6	138.5

Source: Mayo Clinic, Hale et al. 2020, Alzheimer's Association (2022), US Census, and Frost & Sullivan analysis

Table 56. Target Population Size and Prevalence of Mild Cognitive Impairment and Dementia Disorders, United States, Age 50 and older, 2020-2030

Year	Total Population, age 50 and older (million people)	Population, Diagnosed with Dementia (million people)	Population, Diagnosed with Mild Cognitive Decline (No Dementia) (million people)	Age-Related Cognitive Decline, Number of Dementia Transitions per Year (million people)
2021	100.97	6.71	21.13	2.64
2022	103.11	6.82	21.46	2.68
2023	105.25	6.92	21.80	2.72
2024	107.38	7.03	22.13	2.77
2025	109.52	7.13	22.46	2.81
2026	111.66	7.24	22.79	2.85
2027	113.80	7.34	23.12	2.89
2028	115.93	7.45	23.45	2.93
2029	118.07	7.55	23.79	2.97
2030	120.21	7.66	24.12	3.01
Average ('22-'30)	111.66	7.24	22.79	2.85
CAGR	2.0%	1.0%	1.0%	1.5%

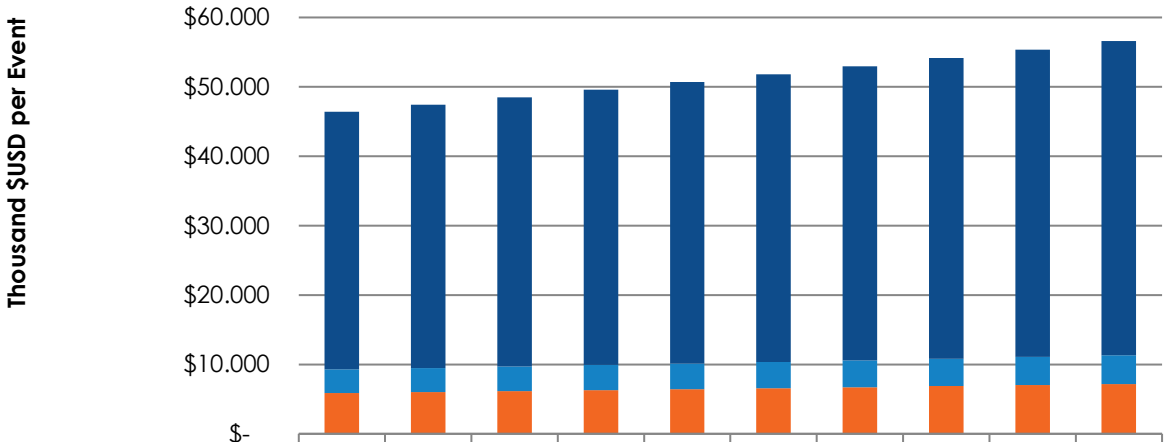
Source: Mayo Clinic, Hale et al. 2020, Alzheimer's Association (2022), US Census, and Frost & Sullivan analysis

There are a wide number of types of tests that physicians and medical practitioners use to assess changes in cognitive performance which in turns to identify severe dementia disorders. For example, the Mini–Mental State Examination (MMSE) or Folstein test is a 30-point questionnaire that is used extensively in clinical and research settings to measure cognitive impairment, and in clinical practice, MMSE is used as a diagnostic tool for dementia [125]. Any score greater than or equal to 24 points (out of 30) indicates normal cognitive performance and below this benchmark, the scores can indicate severe (≤9 points), moderate (10–18 points) or mild (19–23 points) cognitive impairment [125]. The Montreal Cognitive Assessment (MoCA) is a similar cognitive screening tool for mild cognitive impairment [126]. The test assesses concentration, attention, memory, language, calculations, orientation, executive functions and visual skills and a variant of the test is available for illiterate subjects or those who are undereducated. It comprises 30 points like the MMSE and takes 10 minutes to complete. A normal score is considered to be 26 and above. Anyone scoring lower than 26 would require further investigation of their cognitive skills [126]. Activities of Daily Living (ADLs) tests are basic tasks that must be accomplished every day for an individual to thrive.

Understanding how each category affects a person's ability to care for themselves can mean the difference between graceful and independent ageing and needing daily assistance [127,128]. Other tests used to gauge cognitive performance and disability (memory, attention and/or executive functions) and found in nutrition impact assessments includes those of the Wechsler Adult Intelligence Scale, Cambridge Neuropsychological Test Automated Battery (CANTAB), the Verbal Fluency Test (VFT), the Hopkins Verbal Learning Test (HVLT), and the Boston Naming Test (BNT) among others [129,130,131,132,133,134]. Interestingly, some of these tests allow the researcher/clinician to distinguish between normal cognitive decline, mild cognitive decline, and Alzheimer's disease (e.g., Paired Associate Learning (PAL) test of the Cambridge Neuropsychological Test Automated Battery (CANTAB)) [38].

Measuring the economic burden of cognitive impairment bore by Americans includes a mix of both direct medical costs and indirect non-medical costs related to supporting the individual sufferer's quality of life. According to research by the Pharmaceutical Research and Manufacturers of America, the cost of managing the burden of dementia disorders in the US was $259 billion in 2017 [123]. Projecting this figure to 2022 given recent growth in prices and population, it is expected that the cost of managing the burden of dementia disorders in the US was $323.4 billion in 2022 and will be $433.4 billion by 2030. This translates to an average per capita cost of $47,440 per person with diagnosed dementia in 2022, the overwhelming majority of this cost (80%) attributed to cost of disease management which includes hired caregivers, specialized homes, home modifications, etc., and an additional 7% is attributed to specialized pharmaceuticals [123]. It is expected that the overwhelming majority of these cognitive impairment health care costs is directly attributable to Alzheimer disease [121]. Table 57 provides a detailed description of the total and per case medical costs of cognitive impairment in the United States.

Chart 24. Average Health Care Costs per Dementia Patient, Thousand $USD per case, United States, 2020-2030



	'21	'22	'23	'24	'25	'26	'27	'28	'29	'30
Disease Management	$37.1	$38.0	$38.8	$39.7	$40.6	$41.5	$42.4	$43.3	$44.3	$45.3
Pharma	$3.4	$3.5	$3.5	$3.6	$3.7	$3.8	$3.9	$4.0	$4.0	$4.1
Medical	$5.9	$6.0	$6.2	$6.3	$6.4	$6.6	$6.7	$6.9	$7.0	$7.2
Total	$46.4	$47.4	$48.5	$49.6	$50.7	$51.8	$53.0	$54.2	$55.4	$56.6

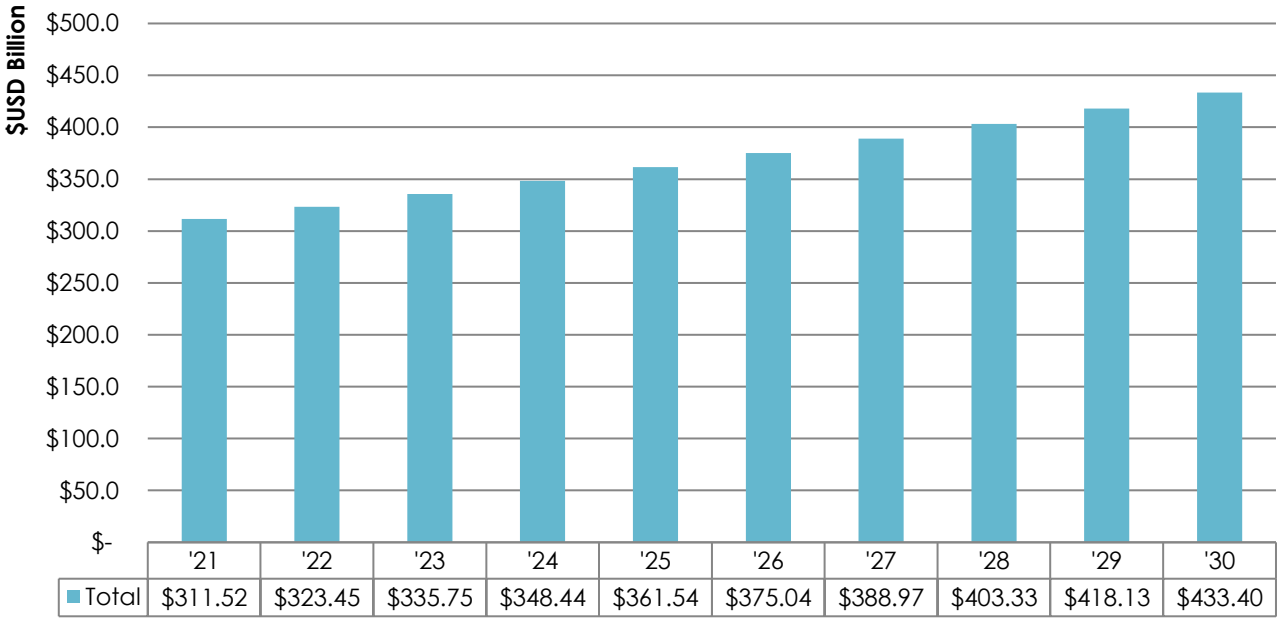
Source: Mayo Clinic, Hale et al. 2020, Alzheimer's Association (2022), US Census, and Frost & Sullivan analysis

Table 57. Health Care Costs per Dementia Patient, Thousand $USD per case, United States, 2020-2030

Year	Age-Related Cognitive Decline, Cost of Disease Management ($ per Event Case)	Age-Related Cognitive Decline, Cost of Medical ($ per Event Case)	Age-Related Cognitive Decline, Cost of Pharma ($ per Event Case)	Age-Related Cognitive Decline, Cost per Event Case ($ per Event Case)	Age-Related Cognitive Decline, Total Cost ($ billion)
2021	$37,123	$5,888	$3,392	$46,404	$311.52
2022	$37,952	$6,020	$3,468	$47,440	$323.45
2023	$38,799	$6,154	$3,546	$48,499	$335.75
2024	$39,666	$6,292	$3,625	$49,582	$348.44
2025	$40,551	$6,432	$3,706	$50,689	$361.54
2026	$41,456	$6,576	$3,788	$51,821	$375.04
2027	$42,382	$6,722	$3,873	$52,977	$388.97
2028	$43,328	$6,873	$3,959	$54,160	$403.33
2029	$44,295	$7,026	$4,048	$55,369	$418.13
2030	$45,284	$7,183	$4,138	$56,605	$433.40
Average ('22-'30)	$41,524	$6,586	$3,795	$51,905	$376.45
CAGR	2.2%	2.2%	2.2%	2.2%	3.7%
Cumulative ('22-'30)					$3,388.05

Source: Mayo Clinic, Hale et al. 2020, Alzheimer's Association (2022), US Census, and Frost & Sullivan analysis

Chart 25. Total Population Health Care Losses Attributed to Dementia Disorders, $USD Billion, United States, 2020-2030



	'21	'22	'23	'24	'25	'26	'27	'28	'29	'30
Total	$311.52	$323.45	$335.75	$348.44	$361.54	$375.04	$388.97	$403.33	$418.13	$433.40

Source: Mayo Clinic, Hale et al. 2020, Alzheimer's Association (2022), US Census, and Frost & Sullivan analysis

Three B vitamins—B6 (pyridoxine), B9 (folate or folic acid), and B12 (cobalamin)—have been extensively studied for their roles in cognitive health [135,136,137]. The interest in these vitamins for reducing cognitive decline stems from their role in metabolizing the amino acid homocysteine, though mechanisms connecting homocysteine levels with cognitive decline are unknown, increased levels of serum homocysteine have been observed among individuals with cognitive decline which suggests a correlation [138,139]. This case study explores the possible health effect and economic benefit that could be expected from the daily use of Vitamin B6, B9 and B12 dietary supplements at effective intake levels as a means to inhibit the rate of cognitive decline to dementia. This will be done by determining the potential cost savings that could be realized given the usage of vitamin B dietary supplements that are scientifically shown to reduce the occurrence of disease-related cognitive decline episodes among adults aged 50 and older. Specifically, this report will attempt to show that using vitamin B dietary supplements by subjects with mild cognitive impairment and thus at risk of developing a more severe dementia disorder can result in health care-related cost savings.

Table 58. Mild Cognitive Impairment and Dementia Demographic Descriptive Statistics for All U.S. Adults Aged 50 and over, 2021–2030

Metric	'21	CAGR ('21 - '30)	Average ('22 - '30)
Total Population, age 50 and older, million people	121.35 M	1.48%	130.86 M
Population with Mild Cognitive Impairment (MCI), million people	21.13 M	1.48%	22.79 M
Population with a Dementia Disorder, million people	6.71 M	1.47%	7.24 M
Event rate—Risk of Individuals with MCI going on to develop a Dementia Disorder, %	12.5%	--	12.5%
Estimated Number of Dementia Transition Events, million people	2.64	1.48%	2.85
Direct Cost of Dementia, Medical Service Utilization, $USD per Case	$5,888	2.23%	$6,586
Direct Cost of Dementia, Pharmaceutical Utilization, $USD per Case	$3,392	2.23%	$3,795
Indirect Cost of Dementia, Disease Management, $USD per Case	$37,123	2.23%	$41,524
Total Cost of Dementia, $USD per Case	$46,404	2.23%	$51,905
Total Target Population Cost of Dementia, $USD billion	$311.5 B	3.74%	$376.5 B
Price Inflation Rate, %	6.95%	--	2.23%

Source: Mayo Clinic, Hale et al. 2020, Alzheimer's Association (2022), US Census, and Frost & Sullivan analysis

Vitamin B6, B9 and B12

Literature Review

The B vitamins B6 (pyridoxine), B9 (folate, folic acid), and B12 (cobalamin) have been extensively studied for their roles in cognitive health [135,136,137]. Many foods are natural sources of these vitamins. For example, B6 is found in cereals, beans, poultry, fish, and some vegetables and fruits, B9 or folate comes from fruits and vegetables, beans, and whole grains, and B12 is found in poultry, fish, red meat, eggs, and dairy products [10].

As stated, the interest in these vitamins for reducing cognitive decline stems from their role in metabolizing the amino acid homocysteine because increased levels of serum homocysteine have been observed among individuals with cognitive decline [138,139]. However, the mechanisms connecting homocysteine levels with cognitive decline remain unknown [138,139]. The analysis in this report is based on studies showing the direct effect on the mean differences of cognitive decline relative to baseline measurements, not on homocysteine as a marker of disease risk.

A 2021 random-effects meta-analysis of 8 studies found that the relative risk of a dementia transition given the use of any combination of dietary vitamins B6, B9 and B12 daily was a statistically significant 90.5% (0.905; 95% CI: 0.805-0.992) [143]. The observed relative risk reduction was also statistically significant (0.095; 95% CI: 0.4%-20.4%). The studies included in the meta-analysis as it relates to the possible benefits of vitamin B dietary supplements on cognitive health is multifaceted as represented by the 8 qualified studies, but the research literature does appear to be converging toward testing the link between the odds of a cognitive decline episode or the relative degree of decline between a non- or low user control group and a high-use or study group [144,145,146,147,148,149,150,151].

Based on the meta-analysis results of the qualified set of scientific studies outlined above, it is expected that the relative risk reduction of a prevalent cognitive decline event, given the supportive daily use of vitamin B dietary supplements, is up to 9.5% according to the set of literature exploring the link between use of vitamin B supplements and the odds of a prevalent cognitive impairment event. The absolute risk reduction from vitamin B supplement use is 1.19% (95% CI: 0.0% - 2.9%) of all prevalent cases of cognitive impairment in the United States, or 84 (95% CI: 40-2767) users per potential benefactor. Furthermore, the number of potential avoided dementia transitions among all American adults with MCI could have been an estimated 258,831 avoided transitions in 2022 had all individuals in the target cohort used vitamin B dietary supplements. Table 59 shows a summary of the key results used to derive the economic implications expected from using vitamins B6, B9 and B12 dietary supplements to support cognitive health.

Table 59. Expected Efficacy of Vitamin B6, B9 and B12 Supplement on Dementia Transition Event Occurrence

Metric	Measure
Relative risk of Cognitive Decline Transition given use of supplement (RR)	0.905 (95% CI: 0.805-0.992)
Relative risk reduction (weighted for intra-study variance) (RRR)	9.5% (95% CI: 0.4%-20.4%)
Absolute risk reduction (ARR)	1.19% (95% CI: 0.0%-2.9%)
Number of people needed to treat to avoid one dementia transition event (NNT), people	84 (95% CI: 40-2767)
Estimated number of events that could have been avoided if the entire target population used vitamins B6, B9 and B12 in 2022	254,895
Average number of events avoided annually if the entire target population used vitamins B6, B9 and B12, 2022-2030	270,642

Source: [143] Shanahan 2021 and Frost & Sullivan analysis

Economic Implications

As stated above, the expected relative risk reduction of a dementia transition event given the use of vitamins B6, B9 and B12 dietary supplements at preventive intake levels was 9.5% and given that 2.68 million people aged 50 and over would have experienced a dementia transition event in 2022, or 12.5% of the target population of people with MCI, 84 people would have needed to use some combination of vitamins B6, B9 and B12 supplements at the daily preventive levels to avoid one dementia transition event. This translates to 254,895 potentially avoidable dementia transition events that could have been saved in 2022 and an average of 270,642 avoided events per year from 2022 to 2030 given current population and disease risk growth expectations.

Subsequently, the expected reduction in health care expenditures in 2022 attributed to avoided dementia transition events would have been $12.09 billion in 2022 based on a person case cost of $47,440 in 2022. Given current population growth, disease risk growth and price inflationary factors, the expected cost savings derived from avoided dementia transition events caused by the use of vitamins B6, B9 and B12 at daily protective intake levels is $14.08 billion per year in total savings from 2022 to 2030.

It is appropriate that the cost of daily use of vitamins B6, B9 and B12 supplements ought to be included in the final accounting. Based on the review of the thirty best-selling retail products currently sold through online sales channels, the median cost of a daily dose of dietary supplements that contains one or more of the vitamins B6, B9 and B12 is approximately $0.20 per day. Given this

daily cost requirement, the median annual expected cost of vitamins B6, B9 and B12 dietary supplementation for all U.S. adults aged 50 and over would be $81.57 per person per year or $1.86 billion per year for the target population over the period 2022 to 2030. Table 60 provides a summary of the cost of dietary supplementation with vitamins B6, B9 and B12 of the entire target population.

Table 60. Vitamin B6, B9 and B12 Cost Savings Analysis: Summary Results—Cost of Dietary Supplementation of the Target Population, 2022-2030

Metric	Measure
Median daily cost per person of Vitamins B6, B9 and B12 supplementation at protective daily intake levels, 2022	$0.20
Expected daily median cost per person of Vitamins B6, B9 and B12 supplementation at protective daily intake levels, 2022-2030	$0.22
Median annual cost per person of Vitamins B6, B9 and B12 supplementation at protective daily intake levels, 2022	$74.51
Expected annual median cost per person of Vitamins B6, B9 and B12 supplementation at protective daily intake levels, 2022-2030	$81.57
Total target population cost of Vitamins B6, B9 and B12 supplementation at protective daily intake levels, 2022	$1.60 B
Total target population cost of Vitamins B6, B9 and B12 supplementation at protective daily intake levels, 2022-2030	$1.86 B

Note: B indicates billion. Source: Frost & Sullivan.

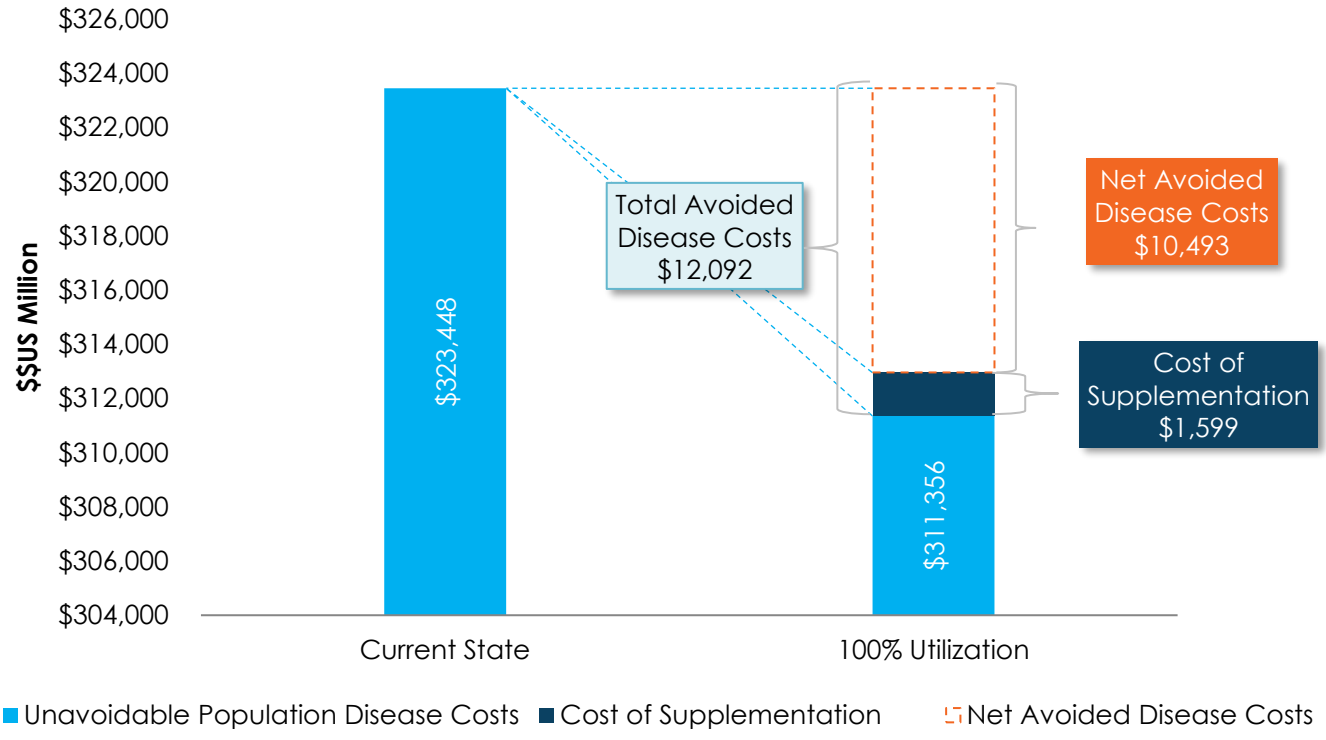
Based the incurred cost of vitamins B6, B9 and B12 dietary supplementation, the net cost savings expected from reduced health care-attributed expenditures in 2022 derived from avoided dementia transition events would have been $10.49 billion in 2022 or $109.93 billion in cumulative net savings during the period 2022 to 2030. Table 61 reports the economic implications of the systematic review finding of the beneficial use of vitamins B6, B9 and B12 supplements to support cardiovascular health.

Table 61. Vitamin B6, B9 and B12 Cost Savings Analysis: Summary Results—Avoided Hospital Utilization Expenditures due to Dietary Supplement Intervention, 2022-2030

Metric	Measure
Avoided Dementia-attributed hospital utilization expenditures given Vitamins B6, B9 and B12 supplement intervention per year, 2022	$12.09 B
Average avoided Dementia-attributed hospital utilization expenditures given Vitamins B6, B9 and B12 supplement intervention per year, 2022-2030	$14.08 B
Net avoided Dementia-attributed hospital utilization expenditures given Vitamins B6, B9 and B12 supplement intervention per year, 2022 (includes cost of supplementation)	$10.49 B
Net average avoided Dementia-attributed hospital utilization expenditures given Vitamins B6, B9 and B12 supplement intervention per year, 2022-2030 (includes cost of supplementation)	$12.22 B
Net benefit cost ratio, $ Savings per one dollar spent on dietary supplement	$7.56
Cumulative net target avoided costs, 2022-2030 (NET BENEFITS) ($ billion)	$109.93 B

Note: B indicates billion. Source: Frost & Sullivan.

Chart 26. Vitamin B6, B9 and B12 Cost Savings Analysis: Health Care Cost Savings from the Use of Health Supplement, 2022 Scenario Analysis



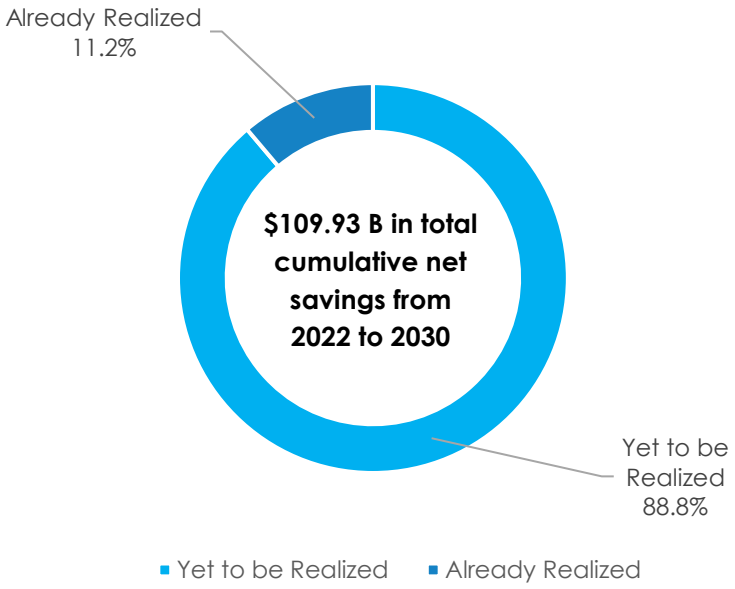
Note: B indicates billion. Source: Frost & Sullivan analysis

The above cost savings results are the maximum savings potential that is obtainable if everyone in the target population (all adults aged 50 and older) had not used this product prior to the base year of analysis (e.g., 2022) and then 100% of the population adopted the vitamins B6, B9 and B12 regimen in the same year and gained all potential benefits. This assumption was made in order to calculate per capita net benefits which in turn can be used to calculate the net avoided cost savings for the subset of the population yet to use vitamins B6, B9 and B12.

Because avoided expenditures and net cost savings are a direct function of the total number of people in the target population using vitamins B6, B9 and B12 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. According to the 2021 Council for Responsible Nutrition Consumer Survey on Dietary Supplements conducted by Ipsos Public Affairs, over 40% of US adults aged 55 and older are regular users of dietary supplements and 26% of supplement users aged 55 and over reported being regular users of vitamins B6, B9 and B12 dietary supplements [152]. This suggests that approximately 11.2% of the total population of US adults aged 55 and older are regular users of vitamin B dietary supplements and the remaining 88.8% of the target population has yet to realize the potential benefits of the supplements' regular use. It should be noted that the target population of this case study includes individuals younger than 55, so the use of these consumer research findings for deducing the proportion of the population yet to realize the benefits from using this supplement is likely underestimated since use of dietary supplements generally increases with age.

Therefore, $9.32 billion of the $10.49 billion in net potential direct savings in 2022 from avoided dementia hospital utilization events because of vitamins B6, B9 and B12 dietary supplement intervention was lost (never realized). If utilization rates go unchanged, an average cost savings opportunity of $10.85 billion per year, or $97.64 billion from 2022 to 2030 in cumulative savings, could be lost because of underutilization of vitamins B6, B9 and B12 dietary supplements. Thus, it is expected that there are still significant cost savings yet be realized through the increased usage of vitamins B6, B9 and B12 dietary supplements among the high-risk target population.

Chart 27. Vitamin B6, B9 and B12 Cost Savings Analysis: Summary Results—Cumulative Net Cost Savings Yet to be Realized due to Avoided Hospital Utilization Expenditures through Dietary Supplement Intervention, 2022-2030



Source: Council for Responsible Nutrition

Table 62. Vitamin B6, B9 and B12 Cost Savings Analysis: Summary Results—Net Cost Savings Yet to be Realized due to Avoided Hospital Utilization Expenditures through Dietary Supplement Intervention, 2022-2030

Metric	Measure
Net avoided dementia-attributed hospital utilization expenditures given Vitamins B6, B9 and B12 supplement intervention yet to be realized per year, 2022	$9.32 B
Net average avoided dementia-attributed hospital utilization expenditures given Vitamins B6, B9 and B12 supplement intervention yet to be realized per year, 2022-2030	$10.85 B
Cumulative net target avoided costs yet realized, 2022-2030 (NET BENEFITS) ($ billion)	$97.64 B

Note: B indicates billion. Source: Frost & Sullivan.

Detailed Results

Table 63. Vitamin B6, B9 and B12 Cost Savings Analysis: Detailed Results—Cost of Dietary Supplementation of the Target Population, 2022-2030

Year	B6, B9 & B12, Daily Cost of Supplementation ($ per day)	B6, B9 & B12, Annual Cost of Supplementation ($ per year)	B6, B9 & B12, Population Cost of Supplementation ($ billion)
2021	$0.20	$72.10	$1.524
2022	$0.20	$74.51	$1.599
2023	$0.21	$76.17	$1.660
2024	$0.21	$78.08	$1.728
2025	$0.22	$79.61	$1.788
2026	$0.22	$81.39	$1.855
2027	$0.23	$83.20	$1.924
2028	$0.23	$85.29	$2.000
2029	$0.24	$86.96	$2.068
2030	$0.24	$88.90	$2.144
Average ('22-'30)	$0.22	$81.57	$1.863
CAGR	2.4%	2.4%	3.9%
Cumulative ('22-'30)			$16.767

Source: Frost & Sullivan.

Table 64. Vitamin B6, B9 and B12 Cost Savings Analysis: Summary Results—Avoided Hospital Utilization Expenditures due to Dietary Supplement Intervention, 2022-2030

Year	B6, B9 & B12 & Age-Related Cognitive Decline, Number of Avoided Events if 100% Utilization by Target User Base (# of Avoided Event Cases)	B6, B9 & B12 & Age-Related Cognitive Decline, Total Target Avoided Costs (BENEFITS) ($ billion)	B6, B9 & B12 & Age-Related Cognitive Decline, Net Target Avoided Costs (NET BENEFITS) ($ billion)	B6, B9 & B12, Benefit/Cost Ratio: $Value of Reduced Risk per $1 spent on Supplement ($/$1 supplement spend)
2021	250,958	$11.646	$10.122	$7.64
2022	254,895	$12.092	$10.493	$7.56
2023	258,831	$12.553	$10.893	$7.56
2024	262,768	$13.029	$11.301	$7.54
2025	266,705	$13.519	$11.731	$7.56
2026	270,642	$14.025	$12.170	$7.56
2027	274,578	$14.546	$12.623	$7.56
2028	278,515	$15.084	$13.084	$7.54
2029	282,452	$15.639	$13.571	$7.56
2030	286,388	$16.211	$14.067	$7.56
Average ('22-'30)	270,642	$14.078	$12.215	$7.56
CAGR	1.48%	3.74%	3.72%	--
Cumulative ('22-'30)	2,435,774	$126.699	$109.932	--

Source: Frost & Sullivan.

Table 65. Vitamin B6, B9 and B12 Cost Savings Analysis: Summary Results—Net Cost Savings Yet to be Realized due to Avoided Hospital Utilization Expenditures through Dietary Supplement Intervention, 2022-2030

Year	B6, B9 & B12 & Age-Related Cognitive Decline, Total Target Avoided Costs Yet to be Realized (BENEFITS) ($ billion)	B6, B9 & B12 & Age-Related Cognitive Decline, Net Target Avoided Costs Yet to be Realized (NET BENEFITS) ($ billion)
2021	$10.34	$8.99
2022	$10.74	$9.32
2023	$11.15	$9.68
2024	$11.57	$10.04
2025	$12.01	$10.42
2026	$12.46	$10.81
2027	$12.92	$11.21
2028	$13.40	$11.62
2029	$13.89	$12.05
2030	$14.40	$12.49
Average ('22-'30)	$12.50	$10.85
CAGR	3.74%	3.72%
Cumulative ('22-'30)	$112.53	$97.64

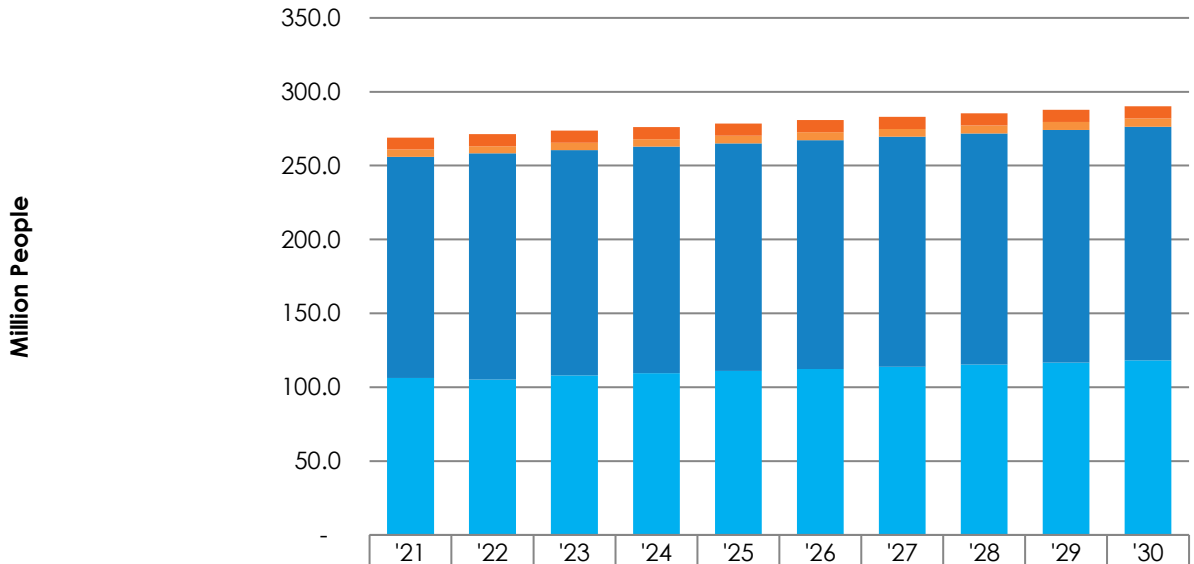
Source: Frost & Sullivan.

LABOR PRODUCTIVITY GAINS FROM THE USE OF PROBIOTICS BY SUFFERERS OF IRRITABLE BOWEL SYNDROME

The Burden and Social Consequences

Irritable Bowel Syndrome (IBS) is a gastrointestinal tract disorder that causes significant abdominal pain to sufferers and can significantly impact quality of life. Due to changes in bowel movement frequency and stool form, IBS leads to higher-than-expected absenteeism from work or school which in turn impacts productivity [156]. IBS puts a heavy burden on sufferers, and they can struggle to cope with its increasing prevalence, as well as the consequential increasing costs of managing the disease condition. IBS affects all Americans of all ages and backgrounds. Specifically, 13.0 million U.S. adults aged 18 and older have IBS, an event risk of 5.0% [157].

Chart 28. Target Population Size and Prevalence of Irritable Bowel Syndrome, United States, Adults Aged 18 and older, 2020-2030



	'21	'22	'23	'24	'25	'26	'27	'28	'29	'30
Employed Adults w/IBS	7.9	8.1	8.1	8.1	8.2	8.2	8.2	8.3	8.3	8.4
Non-working Adults with IBS	5.0	4.9	5.0	5.1	5.2	5.2	5.3	5.4	5.4	5.5
Healthy Employed Adults	149.7	153.0	152.4	153.3	154.1	154.9	155.8	156.6	157.4	158.2
Healthy Non-working Adults	106.2	105.2	108.1	109.5	110.9	112.4	113.8	115.3	116.7	118.2
All Adults Age 18 and Older	256.0	258.2	260.5	262.8	265.0	267.3	269.6	271.8	274.1	276.4

Source: Doshi et al 2014, Palsson et al. 2020, Source: U.S. Bureau of Labor Statistics, US Census, and Frost & Sullivan analysis

Table 66. Target Population Size and Prevalence of Irritable Bowel Syndrome, United States, Adults Aged 18 and older, 2020-2030

Year	Total Population, age 18 and older (million people)	Population of Labor Force (Employment) (million people)	Population, Diagnosed with IBS (million people)	Population of Labor Force (Employment), Diagnosed with IBS (million people)
2021	255.97	157.68	12.90	7.94
2022	258.24	161.14	13.01	8.12
2023	260.50	160.48	13.12	8.08
2024	262.77	161.38	13.23	8.12
2025	265.04	162.26	13.34	8.16
2026	267.31	163.14	13.45	8.21
2027	269.57	164.01	13.56	8.25
2028	271.84	164.87	13.67	8.29
2029	274.11	165.73	13.78	8.33
2030	276.38	166.57	13.89	8.37
Average ('22-'30)	267.31	163.29	13.45	8.21
CAGR	0.9%	0.6%	0.8%	0.6%

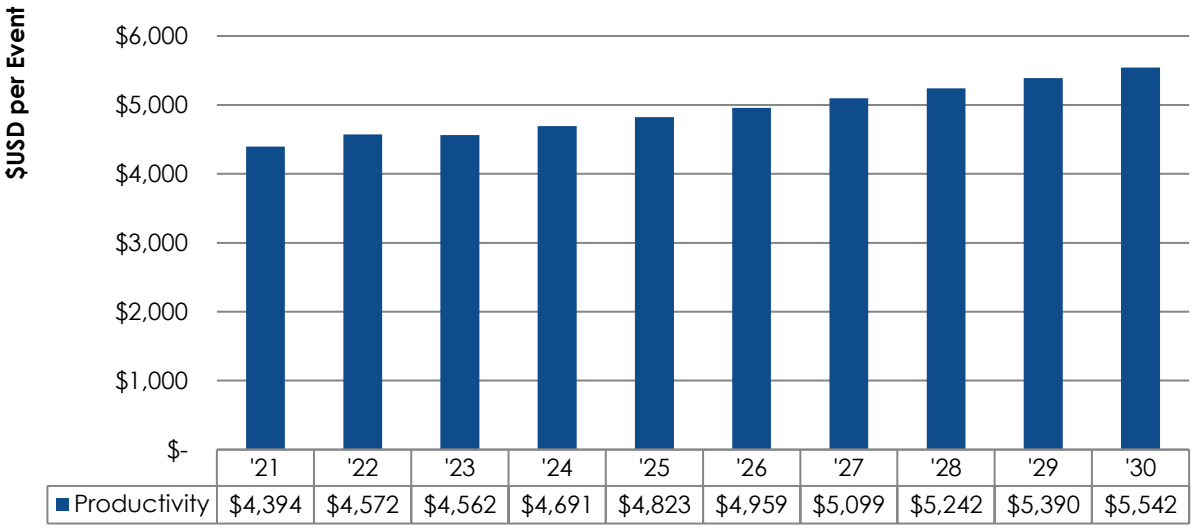
Source: Doshi et al 2014, Palsson et al. 2020, Source: U.S. Bureau of Labor Statistics, US Census, and Frost & Sullivan analysis

Measuring the degree of suffering of IBS patients requires the examination by medical professionals who uses a variety of similar questionnaires to assess self-reported pain and suffering and information regarding abdominal pain, distension, flatulence, and rumbling of the gut are common areas of investigation across the various types of IBS tests available [158]. Common IBS examination scores include the composite IBS symptom score (Total IBS-SSS), Abdominal Pain Severity - Numeric Rating Scale (APS-NRS), Visual Analogue Scale (VAS) for pain ratings, and self-reported Quality of Life (QoL) scores [159]. What is common across all of these scoring systems despite having different scoring ranges is that a higher score typically indicates a greater burden, so any percent reductions in scores can be standardized and compared across related studies using standardized weighted mean differences in severity of symptoms compared to a common baseline.

Researchers from the University of Pennsylvania found that individuals with IBS with constipation paid an additional $6,703 per year on average in additional medical costs compared to non-IBS people and an additional $1,363 per year in 2010 [156]. Productivity losses also add up. Sickness-attributed absenteeism is the phenomenon of missing work due to disability arising from any type of illness or injury which in turn leads to substantial costs to all stakeholders involved including workers who may lose wages, employers who are obligated to pay unproductive wages and even governments in terms of lost tax potential, higher social welfare, and health care costs [160]. In a 2015 survey of Americans who suffer from IBS conducted by Gfk Public Affairs & Corporate

Communications of 3,254 individuals, it was discovered that respondents missed approximately 1.5 days of work or school or month due to IBS-related reasons or an estimated 144 hours per year assuming full employment and an 8-hour work schedule [161].

Chart 29. Average Productivity Losses Caused by Irritable Bowel Syndrome Episode-attributed Absenteeism, $USD per Sufferer per year, United States, 2020-2030



	'21	'22	'23	'24	'25	'26	'27	'28	'29	'30
Productivity	$4,394	$4,572	$4,562	$4,691	$4,823	$4,959	$5,099	$5,242	$5,390	$5,542

Source: U.S. Bureau of Labor Statistics and Frost & Sullivan analysis

In 2022, 161.1 million people aged 18 and older are in the American workforce given an employment rate of 62.4% [162]. In 2022, the average American is expected to have worked 1,708 hours per year (which is equivalent to about nearly 33 hours per week per person) at an average hourly wage of $31.75 per hour [162]. Assuming that the demographic characteristics of IBS sufferers is representative of the American workforce except for the disease state, it is expected that the population of wage earners with IBS in 2022 was 8.12 million individuals aged 18 and older and the value of loss wages due to their IBS absenteeism was $37.1 billion in 2022 and is expected to be an annual average of $41.0 billion per year in productivity losses from 2022 to 2030. The per capita health care costs and productivity losses caused by irritable bowel syndrome episode-attributed absenteeism is shown in Table 67 and the derivation process for the annual value of loss wages due to IBS absenteeism is shown in Table 68.

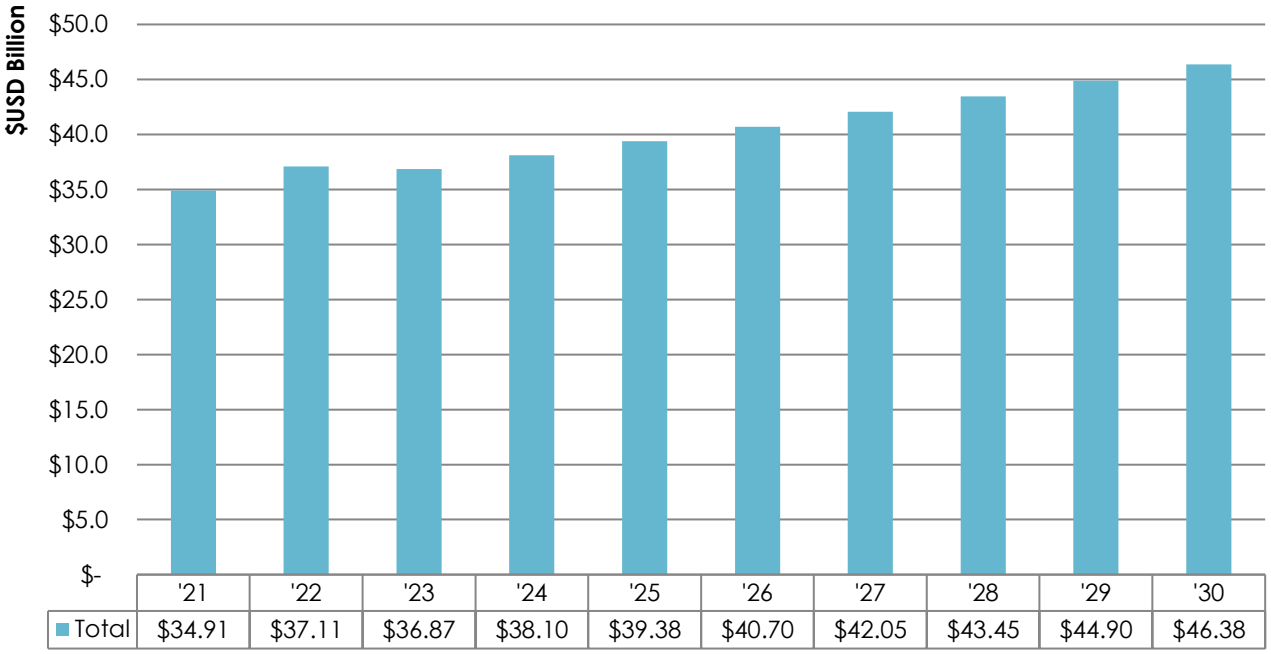
Table 67. Per Capita Health Care Costs and Productivity Losses Caused by Irritable Bowel Syndrome Episode-attributed Absenteeism, $USD per Sufferer per year, United States, 2020-2030

Year	IBS, Cost of Medical ($ per Event Case)	IBS, Cost of Pharma ($ per Event Case)	IBS, Cost per Event Case ($ per Event Case)	IBS, Loss in Productivity ($ per Event Case)	IBS, Population Lost Productive Time Due to IBS Event ($ billion)
2021	$8,513	$1,731	$14,564	$4,395	$34.91
2022	$8,703	$1,770	$14,889	$4,572	$37.11
2023	$8,897	$1,809	$15,221	$4,563	$36.87
2024	$9,096	$1,849	$15,561	$4,691	$38.10
2025	$9,299	$1,891	$15,908	$4,823	$39.38
2026	$9,506	$1,933	$16,263	$4,959	$40.70
2027	$9,718	$1,976	$16,626	$5,099	$42.05
2028	$9,935	$2,020	$16,998	$5,243	$43.45
2029	$10,157	$2,065	$17,377	$5,391	$44.90
2030	$10,384	$2,111	$17,765	$5,542	$46.38
Average ('22-'30)	$9,522	$1,936	$16,290	$4,987	$40.99
CAGR	2.2%	2.2%	2.2%	2.6%	3.2%
Cumulative ('22-'30)					$368.94

Source: U.S. Bureau of Labor Statistics and Frost & Sullivan analysis

Prevention of episodes that leads to absenteeism is critical in minimizing productivity losses. An IBS episode is partially preventable, or its seriousness can be significantly reduced, if the IBS sufferer adopts the use of certain regimens that is known to be effective. One area of growing interest is the role of certain key dietary supplements, especially the role that probiotic supplements, can play in lowering a person's odds of experiencing a severe IBS episode. In this report, a review of the literature that looks at the use of probiotic supplements on the severity of an IBS-attributed episode experienced by sufferers will be undertaken in order to determine the size of the expected health benefit. Then, this expected health benefit will used as a key input in an economic analysis that aims to understand the value of absent time saved due to the relieve in suffering of the IBS workforce.

Chart 30. Total Population Productivity Losses Attributed to Irritable Bowel Syndrome, $USD Billion, United States, 2021-2030



Source: Doshi et al 2014, Palsson et al. 2020, Source: U.S. Bureau of Labor Statistics, US Census, and Frost & Sullivan analysis

Table 68. Productivity Statistics of the American Workforce and the Derivation Process for the Annual Value of Loss Wages due to IBS Absenteeism, 2022

Metric	Measure
Population of labor force (Employment) - million people	161.14 M
Population of labor force (Employment) - % of population	62.4%
Average hourly earnings of all employees, total private - $/hour	$31.75 / hour
Average annual hours worked - hours per Year	1,708 / year
Total US wages - $ billion	$8,741 B
Estimated workforce of people with IBS - million people	8.12 M
Number of hours loss due to IBS-attributed absenteeism per IBS worker	144 hours
Total population productivity losses due to IBS, $USD billion	$37.1 B

Source: Doshi et al 2014, Palsson et al. 2020, Source: U.S. Bureau of Labor Statistics, US Census, and Frost & Sullivan analysis

Table 69. Irritable Bowel Syndrome Cost Summary Statistics for All U.S. Working Adults, Age 18 and over, 2021–2030

Metric	'21	CAGR ('21 - '30)	Average ('22 - '30)
Total workforce, million people	157.68 M	0.61%	163.29 M
Total workforce with IBS, million people	7.94 M	0.58%	8.21 M
Indirect cost of IBS, productivity losses, $USD per sufferer per year	$4,395	2.61%	$4,987
Total productivity losses due to IBS, $USD billion	$34.9 B	3.21%	$41.0 B
Price inflation rate, %	6.95%	--	2.23%

Source: Doshi et al 2014, Palsson et al. 2020, Source: U.S. Bureau of Labor Statistics, US Census, and Frost & Sullivan analysis

A significant amount of clinical research has already been published exploring the association between the use of probiotics by sufferers of IBS for productivity-debilitating symptom relief. In this update study, we examine the potential productivity gains that could be realized if workers with IBS were to regularly use probiotics as a means to reduce productivity-debilitating symptoms. Specifically, this report will examine evidence that demonstrates that the use of probiotics can bring relief to users which in turn can lead to reduced productivity losses associated with absenteeism.

The overarching research methodology used in this economic report is based on a health-to-wealth Cost-Benefit Analysis (CBA) model created in 2013 to address this topic [4]. This model was built to allow the comparison of dietary supplement users versus non-users in terms of any changes in disease-attributed risk which in turn would imply that associated disease treatment and management costs were different as well. Specifically, this CBA can be used to assess various use (and non-use) scenarios and to identify the potential savings or loss that can be realized in one scenario versus another. The determination of whether a given dietary supplement regimen is cost-effective is based on the risk level faced by the user's risk profile, the supplement's effectiveness at reducing the risk of the potential supplement user and the magnitude of the economic consequences (costs) that could be incurred if the potential user did not use the supplement and experienced a medical event [4].

This issue is similar to the basic methodology of most clinical studies; the treatment's effect on the outcome of a given event can be assessed when a treatment regimen is applied to one group versus a control group. From these types of analyses, risk—and possible risk reduction—can be calculated using a cost-benefit model which can be useful to key decision makers (including patients, health

care professionals, governments, insurance companies, and employers) in determining if a given regimen is cost-effective.

To find the true effect size of treatment for a given dietary supplement, a rigorous search for clinical research studies and meta-analyses of clinical research studies for each of the seven interventions was conducted to deduce the expected efficacy of dietary supplementation on the incidence of disease events that required medical treatment and/or resulted in increased costs due to disease management and productivity losses. The aim is to collect a comprehensive set of studies that represented the totality of evidence of efficacy for a given dietary supplement's effects on the relative risk of a specific disease event.

Regarding cost estimate forecasts, expected compound annual growth rates (CAGR) were derived from a historic assessment of population growth rates and price inflation growth. Specifically, health care costs per person are expected to grow at an average annual growth rate of 2.2% from 2022 to 2030 based on the observed average price inflationary growth rate over the last 10 years. Given current inflation rates, we consider this expected growth rate to be conservative. Also, this growth rate was applied for all procedures for all conditions assessed in this study. Growth in the targeted population was expected to occur at the average annual growth rate of the population as a whole 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 were expected to grow at a compound annual growth rate of 2.2% per year, the same as price growth in general. The authors do not endorse the specific findings of any scientific study reviewed.

Probiotics

Literature Review

As defined by the International Scientific Association for Probiotics and Prebiotics (ISAPP), "Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host [163]." Also, "[l]ive microorganisms may be present in many foods and supplements, but only characterized strains with a scientifically demonstrated effect on health should be called probiotics." Gut microbiota must maintain homeostasis to prevent diseases from entering the body. The exact characterization, function, and interaction of microbiota with the host body are important research areas for the development of innovative therapeutic solutions and applications in other industries.

The microbiome refers to the genome of all microorganisms, including symbiotic (benefitting the host and microbiota) and pathogenic (promoting disease), living in humans, animals, and plants. Symbiotic and pathogenic microbiota coexists peacefully in a healthy body, but any disturbance to their coexistence will make the body vulnerable to disease, including in the gut. Microbiota use digestive enzymes to help break down compounds such as starch and fibers. Also, the microbiota can disintegrate indigestible fibers, creating short-chain fatty acids that influence muscle function and prevent chronic diseases, including some bowel disorders.

Live microorganisms may be present in many foods and supplements, however only characterized strains with demonstrated effect on health are termed to be probiotics. Probiotics are generally known by genus, species, and strains. Different strains of the same species have different health effects. The amount of dose administered or consumed is the key as higher doses may not necessarily have a greater health benefit. The dose level should ideally match with the efficacy studies that confer benefits. Probiotics have been researched for decades to prove health benefits, however not all benefits are delivered by just one product or strain.

Lactobacilli and bifodobacteria are the dominate probiotic genera from which most proprietary probiotic strains are based [164]. All other strains make up less than 10% of all probiotics in the marketplace [164]. Hence, the majority of the scientific research on probiotics has used some combination of lactobacilli and bifodobacteria strains in the experimental supplement formulations being tested for gastrointestinal health benefits, though the amount of each strain used in a given formulation and the strain mix used widely varies across studies.

Due to the wide variety of strains and product forms in the marketplace, there is no agreed upon recommended intake level for probiotics. Suggested intake levels depend on strain and target condition. Plus, probiotics are not necessary for use daily, but only when an individual's microbiota is imbalanced. According to the International Probiotics Association, daily doses of 5 to 10 billion

colony forming units (CFUs) has been shown to be effective at reducing antibiotic-associated diarrhea (AAD) in children [165]. With respect to this study's systematic review, the typical (mode) dose size to help reduce severity of IBS-attributed pain is 10 billion CFUs per day of required use.

Overall, the breadth and depth of scientific research exploring the association between use of probiotics and the severity in IBS-attributed discomfort is significant. However, the literature is quite heterogeneous with respect to study design, types of effect sizes measured, dose size, strain types and mixes, and types of IBS. In 2016, Ford et al. conducted a meta-analysis of 43 RCTs and found that the RR of IBS symptoms persisting among probiotic users versus placebo was 0.79 (95% CI 0.70-0.89). This means that over 20% more people reported relief in the probiotic group compared to the placebo group [166]. In 2014, researchers found that quality of life of IBS sufferers improved significantly among probiotic users versus placebo (IBS-QoL 18 ± 3 points (P = 0.041) and 22 ± 4 points (P = 0.023) in the high and the low dose groups, respectively [167].

To infer the expected efficacy of using probiotics on reducing the severity of an IBS episode that motivates absenteeism, a literature review was conducted in December 2021 that focused on published studies that directly tested for and quantified the effect of Probiotic supplementation on the severity of IBS episodes reported by sufferers. The goal of this study was to collect a comprehensive sample of studies that represented the state of all scientific literature on Probiotic supplementation as it related to reducing self-reported gastrointestinal pain among individuals diagnosed with IBS. It was preferred that the selected studies were similar in study protocol in an attempt to control for likely differences in study protocol, though this is not always possible due to the nature of this body of research being highly heterogeneous with respect to types of probiotic strains used in the formulations. Specifically, of the various study methods found for probiotic 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.

One hundred forty-nine (149) studies were found in a PubMed search based on the use of "probiotic" or "supplement" and "irritable bowel syndrome" and "pain" as filtering keywords. The search was conducted between December 1, 2021, and May 31, 2022. After reviewing all studies' titles, abstracts, and full-texts, 19 RCTs consisting of 24 test arms were identified as being representative of the hypothesis being tested and these studies were used to deduce the estimated efficacy of using any probiotic supplement on reducing IBS-related gastrointestinal pain. Tables 70 and 71 provide a description of the selection of included studies in the final meta-analysis described below.

Table 70. Probiotics Literature Review: Description of the Qualified Studies

REF.	Author	Publication Year	Event definition	Product Description
168	Skrzydło-Radomańska B	2021	Total IBS-SSS	A mixture of Lactobacillus, Bifidobacterium, and Streptococcus thermophilus
169	Lewis ED	2020	Total IBS-SSS	L. paracasei
169	Lewis ED	2020	Total IBS-SSS	B. longum
170	Martoni CJ	2020	APS-NRS Score	L. acidophilus DDS-2
170	Martoni CJ	2020	APS-NRS Score	B. lactis UABla-13
170	Martoni CJ	2020	Total IBS-SSS	L. acidophilus DDS-2
170	Martoni CJ	2020	Total IBS-SSS	B. lactis UABla-13
171	Sadrin S	2020	VAS Composite	2-strain mixture of Lactobacillus acidophilus
172	Oh JH	2019	Abdominal pain (VAS)	mixture of lactobacilli probiotics
173	Preston K	2018	QoL Improvement	A combination of Lactobacillus acidophilus CL1285, Lactobacillus casei LBC80R and Lactobacillus rhamnosus CLR2
159	Lyra A	2016	Severity of pain	One capsule per day containing either 109 (low dose) or 1010 (high dose) CFU of L. acidophilus NCFM (ATCC 700396).
174	Stevenson C	2014	QoL Improvement	Two capsules of L. plantarum 299v
175	Lorenzo-Zúñiga V	2014	QoL Improvement	Combination of three strains of lactic acid bacteria: two Lactobacillus plantarum (CECT7484 and CECT7485) and one Pediococcus acidilactici (CECT7483)
175	Lorenzo-Zúñiga V	2014	QoL Improvement	Combination of three strains of lactic acid bacteria: two Lactobacillus plantarum (CECT7484 and CECT7485) and one Pediococcus acidilactici (CECT7483)
176	Yoon JS	2014	Abdominal pain	Patients were randomly assigned to two groups: either to receive multi-species probiotics (a mixture of Bifidobacterium longum, Bifidobacterium bifidum, Bifidobacterium lactis, Lactobacillus acidophilus, Lactobacillus rhamnosus, and Streptococcus thermophilus) twice a day for four weeks, or to receive a placebo twice a day for four weeks.
177	Ducrotté P	2012	Abdominal pain (VAS)	L. plantarum 299v
178	Ki Cha B	2012	VAS Composite	Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus rhamnosus, Bifidobacterium breve, Bifidobacterium lactis, Bifidobacterium longum, and Streptococcus thermophilus 1.0 1010 CFU) groups
179	Williams EA	2009	Total IBS-SSS	Lactobacillus acidophilus CUL60 (NCIMB 30157) and CUL21 (NCIMB 30156), Bifidobacterium lactis CUL34 (NCIMB 30172) and Bifidobacterium bifidum CUL20 (NCIMB 30153)
180	Sinn DH	2008	Abdominal pain	Lactobacillus acidophilus-SDC 2012, 2013
181	Kajander K	2008	Total IBS-SSS	Lactobacillus rhamnosus GG, L. rhamnosus Lc705, Propionibacterium freudenreichii ssp. shermanii JS and Bifidobacterium animalis ssp. Lactis Bb12
182	Whorwel, P	2006	Abdominal pain or discomfort	B. longum 35624
183	O'Mahony L	2005	VAS Composite	B. longum 35624

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

Table 71. Probiotics Literature Review: Description of the Qualified Studies (continued)

REF.	Author	Dose Size (CFU billion)	Study Duration (Days)	Sample Size	Treatment Group Size	Control Group Size
168	Skrzydło-Radomańska B	250	56	48	25	23
169	Lewis ED	10	56	165	84	81
169	Lewis ED	10	56	164	83	81
170	Martoni CJ	10	42	220	111	109
170	Martoni CJ	10	42	219	110	109
170	Martoni CJ	10	42	220	111	109
170	Martoni CJ	10	42	219	110	109
171	Sadrin S	10	56	80	40	40
172	Oh JH	10	28	50	26	24
173	Preston K	50	84	85	58	27
159	Lyra A	10	84	228	110	118
174	Stevenson C	5	70	81	54	27
175	Lorenzo-Zúñiga V	20	42	56	27	29
175	Lorenzo-Zúñiga V	200	42	57	28	29
176	Yoon JS	10	28	49	25	24
177	Ducrotté P	10	28	204	105	99
178	Ki Cha B	10	56	50	25	25
179	Williams EA	250	56	52	28	24
180	Sinn DH	10	28	40	20	20
181	Kajander K	6	140	86	43	43
182	Whorwell P	0.1	28	182	90	92
183	O'Mahony L	10	56	64	25	25

Note: Dose size as measured by CFU should not be used as an indication of strength of efficacy. Efficacy and CFU varies by strain type. All figures are rounded. Source: Frost & Sullivan

Clinical research in the probiotic for gastrointestinal health remains an active field of clinical research and a number of studies demonstrating probiotic supplement's efficacy has been published just within the last decade. A 12-week study consisting of 340 IBS adult volunteers in 2016 explored the efficacy of using Lactobacillus acidophilus on IBS symptoms and quality of life (QoL) [159]. The researchers found that IBS-SSS improved over a 12-week treatment in volunteers with moderate to severe abdominal pain at baseline (VAS > 35/100) [159]. Specifically, pain scores fell by 29.4 ± 17.9and 31.2 ± 21.9 in the placebo, active low-dose, and active high-dose groups versus the 20.8 ± 22.8 in the control group respectively (P value for placebo versus combined active doses = 0.046) [159].

In 2019, researchers in Vietnam invested whether use of a mixture of lactobacilli probiotics could improve abdominal symptoms in subjects with IBS [172]. Once a day, 50 subjects took either a placebo or a probiotic supplement based on a mixture of lactobacilli strains and abdominal pain visual analogue scale was assessed after 4 weeks of use [172]. The study found that use of lactobacilli-based probiotics significantly improved observed VAS scores in the probiotic group (p = 0.048) [172].

And in 2018, researchers reported that self-reported quality of life was improved among IBS users of probiotic supplements based on the strains Lactobacillus acidophilus CL1285, Lactobacillus casei LBC80R and Lactobacillus rhamnosus CLR2 [173]. Specifically, 113 subjects were randomized into two groups and given either a placebo or a probiotic supplement formulation using the aforementioned strains at a 50×109 CFU concentration daily for 12 weeks [173]. The key finding from this study was that quality of life was improved, especially when it came to stool frequency and consistency among the treatment group [173].

Researchers in 2020 reported the results of their double-blind RCT that included 336 subjects aged 18 to 70 which investigated the efficacy of two probiotic strains on both abdominal pain severity (APS-NRS) and total IBS-SSS score from baseline [170]. Subjects with IBS according to Rome IV criteria were either provided for 6 weeks a placebo, a supplement containing Lactobacillus acidophilus DDS-1 (1 × 1010 CFU/day) or a supplement containing Bifidobacterium animalis subsp. lactis UABla-12 (1 × 1010 CFU/day) [15]. APS-NRS was significantly improved in both probiotic groups vs. placebo in absolute terms (DDS-1: -2.59 ± 2.07, p = 0.001; UABla-12: -1.56 ± 1.83, p = 0.001) and improvement was observed in IBS Symptom Severity Scale (IBS-SSS) scores for L. acidophilus DDS-1 (-133.4 ± 95.19, p < 0.001) and B. lactis UABla-12 (-104.5 ± 96.08, p < 0.001) groups vs. placebo [170].

Also in 2020, scientists explored the effectiveness of two probiotic supplement formulations based on Lactobacillus paracasei HA-196 (L. paracasei) and Bifidobacterium longum R0175 (B. longum), respectively, on reducing physical and psychological symptoms of IBS [14]. Two hundred fifty-one adults were randomized to take one of the two different probiotic supplements or a placebo for 4-

and 8-week study durations [169]. The researchers found that use of L. paracasei-based probiotic supplements improved regularity in people with both IBS-constipation (IBS-C) and IBS-diarrhea (IBS-D) and both formulations significantly improved self-reported quality-of-life in emotional well-being baseline ($p < 0.05$) [169].

Another study published in 2020 aimed to show that a two-strain mixture of Lactobacillus acidophilus improved irritable bowel syndrome symptoms, as proxied by an abdominal pain score assessed with a 100-mm visual analogue scale (VAS) among users versus placebo users [171]. In this 8-week study, 80 subjects were randomized into either the control group or the treatment group who were provided two capsules containing either Lactobacillus acidophilus probiotics at a concentration of 5 × 109 cfu per capsule daily [171]. The scientists found that the abdominal pain score between the two groups were not significantly different but that the probiotic treatment group did have improvement in the visual analogue scale (VAS) score after 8 weeks [171].

In 2021, researchers released the results of an RCT study that explored the efficacy of multi-strain probiotic in adults with diarrhea-predominant irritable bowel syndrome (IBS-D) [168]. The multi-strain probiotic supplement contained a mixture of Lactobacillus, Bifidobacterium, and Streptococcus thermophilus strains and the study duration was 8 weeks [168]. Use of the multi-strain probiotic supplement significantly improved the IBS symptom severity (the change of total IBS-SSS score from baseline –165.8 ± 78.9 in the probiotic group versus –105.6 ± 60.2 in the placebo group, $p = 0.005$) and secondary end points also demonstrated that the severity of pain ($p = 0.015$) and the quality-of-life ($p = 0.016$) improved in the treatment group after eight weeks [168].

To deduce the effect of using probiotics on reducing the severity of an IBS episode that motivates absenteeism, a random-effects meta-analysis model was developed which is best model for deducing the true treatment effect from a set of clinical research citations that varies by sample size, methodologies and study protocols, and patient population dynamics [184, 185]. This approach allows for a systematic and objective approach to weighing each of the qualified reported effects sizes [184, 185].

Based on applying the random-effects meta-analysis model to the qualified set of clinical studies described above, it is expected that the weighted standard mean difference (WSMD) in the severity of reported IBS episodes by those using probiotic supplements, or the reported Cohen's d score, is 0.516 (95% CI: 0.200 – 0.833) after controlling for variance caused by study sample size, research protocols, and patient population differences within each study and among all studies. A Cohen's d effect size score is a way to standardize similar types of tests into one overarching expected effect size. All of the different types of quality-of-life scales used by the researchers in the eligible studies measured the mean difference in pain and/or quality of life scores before and after treatment and, independent of the scoring system used, it would be expected that the distribution of IBS severity

would be different between the user group and the non-user group. It can be shown that an effect size of 0.516 means that approximately 65.3% of the treatment population are feeling similar levels of discomfort and pain as the participants in the control group and that 34.7% (95% CI: 15.2%-49.8%) of the treatment group is feeling equal to or better than the best feeling person in the control group [186]. Thus, 34.7% of probiotic supplement users with chronic IBS feel better and have an improved quality of life than the best-off person in the control group.

Given the nature of the disorder, the goal of managing IBS is to increase quality of life so that the individual can have a much more productive life. The topic of absenteeism caused by IBS is a good way to understand the direct economic impact of IBS as researchers first did in 2014 which estimated that the average number of days a worker with IBS is absent from work per month due to IBS-attributed symptoms was 1.5 days per month (or 144 hours per year) [161]. Since it is expected that 34.7% of the target population will experience improvements in symptoms, this portion of the population will be able to fully work and hence will not contribute to the average number of hours lost per year to absenteeism. In other words, a 34.7% reduction in absenteeism can be expected per user which is equivalent to a savings in 50.0 hours per year per user. Given that there are 7.94 million potential benefactors in the total workforce with IBS, this amounts to a total population potential of 397.38 million hours if all employees with IBS utilized probiotics during an IBS event. Table 72 describes the empirical results of the included studies in the final systematic review and Table 73 reports the aggregated expected effect size of probiotics use on reducing the severity of an IBS episode.

Table 72. Probiotics Literature Review: Summary of Study Findings

REF.	Author	Standardized Mean Difference (Cohen's d, Improvement Effect Size)	95% Low	95% High
168	Skrzydło-Radomańska B	0.81	0.53	1.10
169	Lewis ED	0.06	-0.09	0.21
169	Lewis ED	-0.45	-0.60	-0.29
170	Martoni CJ	0.35	0.22	0.49
170	Martoni CJ	0.26	0.13	0.39
170	Martoni CJ	0.52	0.39	0.65
170	Martoni CJ	0.08	-0.05	0.21
171	Sadrin S	0.37	-0.23	0.21
172	Oh JH	3.70	1.29	1.85
173	Preston K	0.30	-0.17	0.26
159	Lyra A	0.14	0.01	0.27
174	Stevenson C	0.46	0.24	0.68
175	Lorenzo-Zúñiga V	1.56	1.30	1.82
175	Lorenzo-Zúñiga V	0.39	0.13	0.65
176	Yoon JS	0.39	0.11	0.67
177	Ducrotté P	0.05	0.01	0.28
178	Ki Cha B	1.46	1.18	1.73
179	Williams EA	3.42	3.14	3.69
180	Sinn DH	0.32	0.01	0.63
181	Kajander K	4.65	4.23	4.65
182	Whorwell P	1.36	1.40	1.32
183	O'Mahony L	0.44	0.38	0.50

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

Table 73. Expected Efficacy of Supplement Use Based on Literature Review, Probiotics

Metric	Measure
Standardized Weighted Mean Difference (weighted for intra-study variance) (WMD)	0.516 (95% CI: 0.200 – 0.833)
% Overlap of self-reported IBS discomfort distribution between the Treatment Group and Control Group, %	65.3% (95% CI: 50.2%-84.8%)
% of Treatment Group who feel better than the Control Group with respect to self-reported IBS discomfort, %	34.7% (95% CI: 15.2%-49.8%)
Number of Avoided Absentee Hours Lost due to IBS discomfort per Probiotic User, hours per user	50.2 hours
Potential number of Avoidable Absentee Hours for the labor population with IBS, total avoidable hours	397.38 M hours

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

Economic Implications

As already highlighted in the previous section, it is expected that the population of wage earners with IBS in 2022 was 8.12 million individuals aged 18 and older and the value of loss wages due to their IBS absenteeism was $37.1 billion in 2022 and is expected to be an annual average of $41.0 billion per year in productivity losses from 2022 to 2030. If 100% of the target population of IBS suffering wage earners used probiotic supplements consistently, the total potential savings in lost productivity due to avoiding 50.2 absentee hours per year per person would have been 650.6 million hours valued at $12.89 billion in 2022. From 2022 to 2030, the annual average in total potential saved wages will be $14.24 billion during the forecast period.

The daily cost of using probiotic supplements ought to be included in the final accounting in order to ensure that all cost components are considered in the final analysis. Based on the review of the best-selling retail probiotic supplement products currently sold through online sales channels, the median cost of a daily dose of probiotics is approximately $0.61 per day. Given this daily cost requirement, the median annual expected cost of probiotics dietary supplementation for all U.S. adults aged 18 and over would be $241.80 per person per year or $1.99 billion per year for the total target population of wage earners with IBS over the period 2022 to 2030. Table 74 provides a summary of the cost of dietary supplementation with probiotics of the entire target population.

Table 74. Probiotics Productivity Gains Analysis: Summary Results—Cost of Dietary Supplementation of the Target Population*, 2022-2030

Metric	Measure
Median daily cost per person of Probiotic supplementation at protective daily intake levels, 2022	$0.61
Expected daily median cost per person of Probiotic supplementation at protective daily intake levels, 2022-2030	$0.66
Median annual cost per person of Probiotic supplementation at protective daily intake levels, 2022	$220.98
Expected annual median cost per person of Probiotic supplementation at protective daily intake levels, 2022-2030	$241.78
Total target population cost of Probiotic supplementation at protective daily intake levels, 2022	$1.79 B
Total target population cost of Probiotic supplementation at protective daily intake levels, 2022-2030	$1.99 B

Table 75 reports the economic implications of the systematic review finding of the beneficial use of Probiotic supplements to support cardiovascular health. Given the incurred cost of probiotics dietary supplementation, the net Productivity Gains expected from avoided absenteeism caused by severe IBS episodes would have been $11.10 billion in 2022 or $12.25 billion per year in net savings during the period 2022 to 2030. The above productivity gains results are the maximum savings potential that is obtainable if everyone in the target population (all adults aged 18 and older) had not used this product prior to the base year of analysis (e.g., 2022) and then 100% of the population adopted the probiotics regimen in the same year and gained all potential benefits. This assumption was made in order to calculate per capita net benefits which in turn can be used to calculate the net avoided productivity gains for the subset of the population yet to use probiotics. It follows that the calculation of avoided health care expenditures and net productivity gains yet to be realized is simply a proportional adjustment of the total potential avoided expenditures and net productivity gains.

Chart 31. Probiotics Productivity Gains Analysis: Labor Productivity Gains from the Use of Probiotic Supplements, 2022 Scenario Analysis

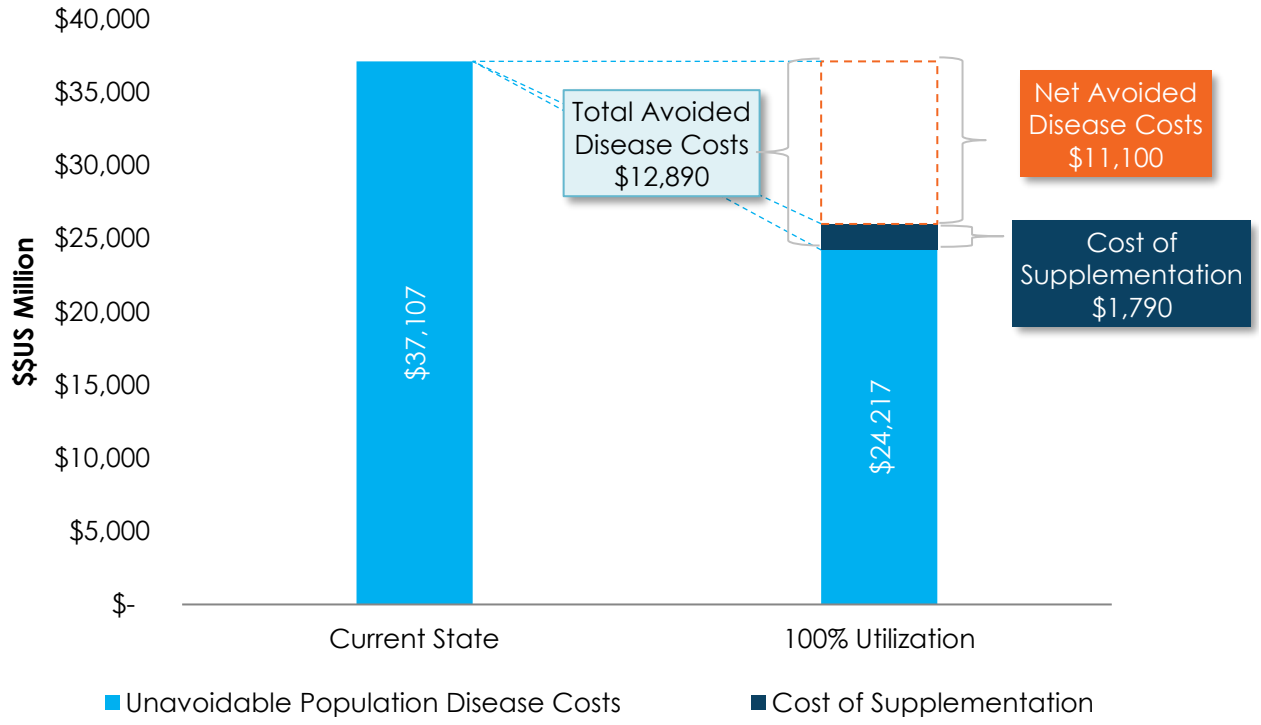
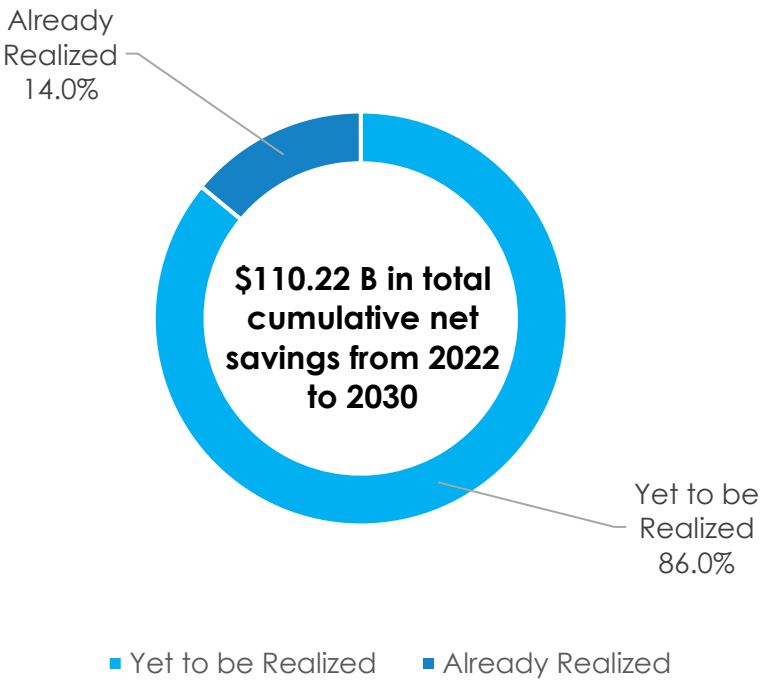


Table 75. Probiotics Productivity Gains Analysis: Summary Results—Avoided Productivity Losses due to Dietary Supplement Intervention, 2022-2030

Metric	Measure
Avoided loss wages from IBS-attributed absenteeism given Probiotic supplement intervention per year, 2022	$12.89 B
Average avoided loss wages from IBS-attributed absenteeism given Probiotic supplement intervention per year, 2022-2030	$14.24 B
Net avoided loss wages from IBS-attributed absenteeism given Probiotic supplement intervention per year, 2022 (includes cost of supplementation)	$11.10 B
Average net avoided average avoided Loss Wages from IBS-attributed absenteeism given Probiotic supplement intervention per year, 2022-2030 (includes cost of supplementation)	$12.25 B
Net benefit cost ratio, $ Savings per one dollar spent on dietary supplement	$7.16
Cumulative Net Target Avoided Costs, 2022-2030 (NET BENEFITS) ($ billion)	$110.22 B

Today, the use of Probiotic supplements remains relatively low. According to the 2021 Council for Responsible Nutrition Consumer Survey on Dietary Supplements conducted by Ipsos Public Affairs, 14% of U.S. dietary supplement users aged 18 and over have used probiotics dietary supplements in the last 12 months [152]. Also, over 40% of US adults aged 18 and older are regular users of dietary supplements which implies that only 5.6% of the target population aged 18 and over reported using probiotics in the last months [152].

Chart 32. Probiotics Productivity Gains Analysis: Summary Results—Cumulative Net Productivity Gains Yet to be Realized due to Avoided Loss Wages through Probiotic Supplement Intervention, 2022-2030



Source: Council for Responsible Nutrition

Consequently, $9.54 billion of the $11.10 billion in net potential direct savings in 2022 from avoided loss wages because of probiotic supplement intervention will not be gained. If utilization rates go unchanged, an average productivity gains opportunity of $10.54 billion per year could be lost because of underutilization of probiotic dietary supplements. In conclusion, this case study's findings support the proposition that utilization of a probiotic supplement can help in lowering a person's odds of experiencing a severe IBS episode which in turn can lead to positive knock-on effects on the costs of labor productivity. Accordingly, adopting new regimens or routines that have been shown to help to minimize IBS-related episodes that a person might experience and pay for in terms of lost work hours ought to be considered.

Table 76. Probiotics Productivity Gains Analysis: Summary Results—Net Productivity Gains Yet to be Realized due to Avoided Productivity Losses through Dietary Supplement Intervention, 2022-2030

Metric	Measure
Net avoided loss wages from IBS-attributed absenteeism given Probiotic supplement intervention yet to be realized per year, 2022	$9.54 B
Average net avoided loss wages from IBS-attributed absenteeism given Probiotic supplement intervention yet to be realized per year, 2022-2030	$10.54 B
Cumulative net loss wages from IBS-attributed absenteeism yet to be realized, 2022-2030 (NET BENEFITS) ($ billion)	$94.83 B

Detailed Results

Table 77. Productivity Statistics of the American Workforce, 2022 – 2030

Year	Average Annual Hours Worked (Hours per Year)	Average Hourly Earnings of All Employees, Total Private ($/hour)
2021	1713.31	30.52
2022	1708.46	31.75
2023	1703.61	31.68
2024	1698.76	32.58
2025	1693.91	33.50
2026	1689.06	34.44
2027	1684.21	35.41
2028	1679.36	36.41
2029	1674.51	37.43
2030	1669.66	38.49
Average ('22-'30)	1689.06	34.63
CAGR	-0.3%	2.6%

Source: Frost & Sullivan

Table 78. Probiotics Productivity Gains Analysis: Detailed Results—Cost of Dietary Supplementation of the Target Population, 2022-2030

Year	Probiotics, Daily Cost of Supplementation ($ per day)	Probiotics, Annual Cost of Supplementation ($ per year)	Probiotics, Population Cost of Supplementation ($ billion)
2021	$0.59	$216.05	$1.716
2022	$0.61	$220.98	$1.793
2023	$0.62	$225.91	$1.825
2024	$0.63	$230.96	$1.876
2025	$0.65	$236.11	$1.928
2026	$0.66	$241.39	$1.981
2027	$0.68	$246.77	$2.035
2028	$0.69	$252.28	$2.091
2029	$0.71	$257.92	$2.148
2030	$0.72	$263.67	$2.207
Average ('22-'30)	$0.66	$241.78	$1.987
CAGR	2.2%	2.2%	2.8%
Cumulative ('22-'30)	--	--	$94.561

Source: Frost & Sullivan

Table 79. Probiotics Productivity Gains Analysis: Detailed Results—Avoided Productivity Losses due to Dietary Supplement Intervention, 2022-2030

Year	Probiotics & IBS, Total Target Avoided Loss Wages (BENEFITS) ($ billion)	Probiotics & IBS, Net Target Avoided Loss Wages (NET BENEFITS) ($ billion)	Probiotics & IBS, Benefit/Cost Ratio: $Value of Reduced Risk per $1 spent on Supplement ($/$1 supplement spend)
2021	$12.13	$10.41	$6.08
2022	$12.89	$11.10	$6.18
2023	$12.81	$10.98	$6.03
2024	$13.24	$11.36	$6.07
2025	$13.68	$11.75	$6.10
2026	$14.14	$12.16	$6.14
2027	$14.61	$12.57	$6.17
2028	$15.09	$13.00	$6.21
2029	$15.60	$13.45	$6.24
2030	$16.11	$13.91	$6.28
Average ('22-'30)	$14.24	$12.25	$6.16
CAGR	3.21%	3.27%	$0.00
Cumulative ('22-'30)	$128.16	$110.22	

Source: Frost & Sullivan

Table 80. Probiotics Productivity Gains Analysis: Detailed Results— Net Productivity Gains Yet to be Realized due to Avoided Productivity Losses through Dietary Supplement Intervention, 2022-2030

Year	Probiotics & IBS, Total Target Avoided Loss Wages Yet to be Realized (BENEFITS) ($ billion)	Probiotics & IBS, Net Target Avoided Loss Wages Yet to be Realized (NET BENEFITS) ($ billion)
2021	$10.43	$8.95
2022	$11.08	$9.54
2023	$11.01	$9.44
2024	$11.38	$9.77
2025	$11.76	$10.11
2026	$12.16	$10.45
2027	$12.56	$10.81
2028	$12.98	$11.18
2029	$13.41	$11.56
2030	$13.86	$11.96
Average ('22-'30)	$12.25	$10.54
CAGR	3.21%	3.27%
Cumulative ('22-'30)	$110.22	$94.83

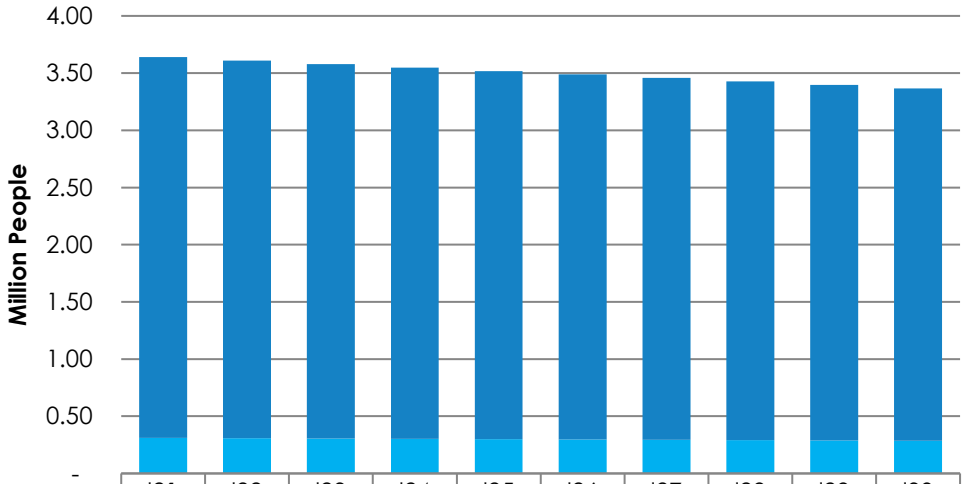
Source: Frost & Sullivan

REDUCTION IN EARLY CHILDHOOD COGNITIVE DEVELOPMENT DISORDERS DUE TO INADEQUATE MATERNAL CHOLINE INTAKE DURING PREGNANCY FROM CHOLINE SUPPLEMENT USE

The Burden and Social Consequences

It is becoming increasingly clear that adequate intake of choline by expectant mothers is critical for the optimal cognitive development of their children yet inadequate intake of choline among expectant mothers is highly common. In fact, over 90% of expectant mothers do not consume enough choline daily through their normal diet according to findings from NHANES [185]. Consequently, delegates of the American Medical Association voted in 2017 to support the recommendation that evidence-based amounts of choline should be included in all prenatal vitamins based on the significant amounts of scientific research that shows that adequate amounts of choline is critical for the baby's brain and spinal cord properly development after birth and is also critical for ensuring normal neural development of the fetus and reducing the incidence of birth defects [186,187,188,189].

Chart 33. Target Mother Population Size and Prevalence of Inadequate Maternal Choline Intake, 13 to 44 years old, United States, 2021-2030



	'21	'22	'23	'24	'25	'26	'27	'28	'29	'30
Choline Deficient Mothers	3.33	3.30	3.27	3.25	3.22	3.19	3.16	3.14	3.11	3.08
Choline Sufficient Mothers	0.31	0.31	0.30	0.30	0.30	0.30	0.29	0.29	0.29	0.29
All Mothers	3.64	3.61	3.58	3.55	3.52	3.49	3.46	3.43	3.40	3.37

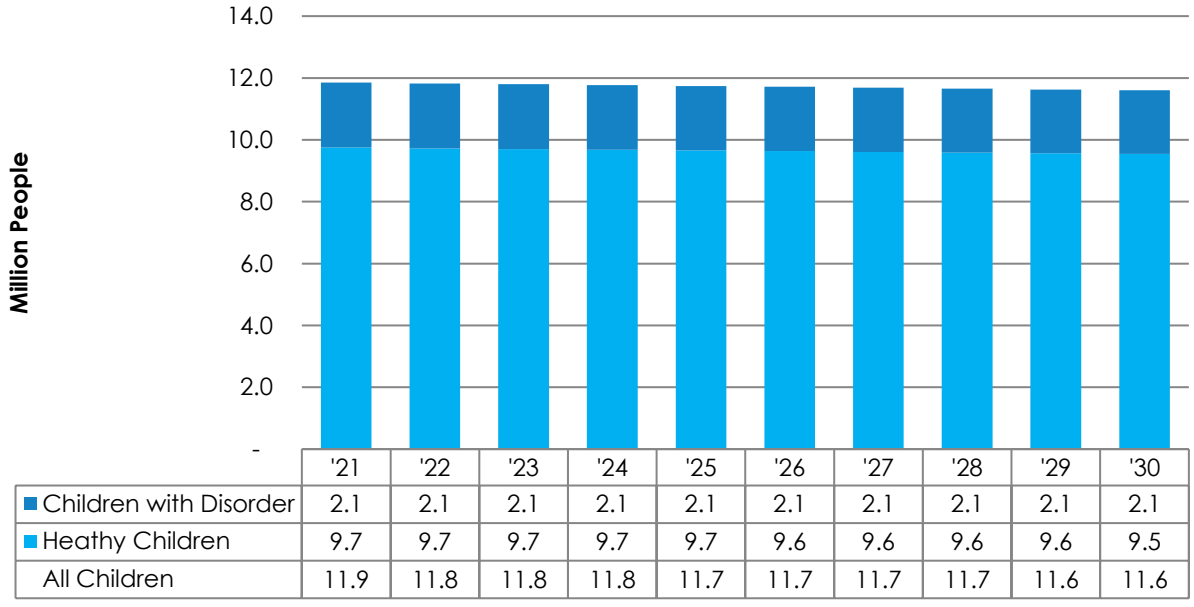
Source: Wallace et al. 2017m, Korsmo et al. 2019, Derbyshire et al. 2020. Centers for Disease Control and Prevention, US Census, and Frost & Sullivan analysis

Table 81. Target Population Size and Prevalence of Inadequate Maternal Choline Intake, Mother: 13 to 44 years old and Children: 3 to 8 years old, United States, 2021-2030

Year	Inadequate Maternal Choline Intake & Postnatal Neurocognitive Development, Child Population age 3 to 8 years old (million people)	Population, Mental health diagnosis, age 3 to 8 years old (million people)	Inadequate Maternal Choline Intake & Postnatal Neurocognitive Development, Mother Population (million people)
2021	11.85	2.10	3.64
2022	11.82	2.10	3.61
2023	11.80	2.09	3.58
2024	11.77	2.09	3.55
2025	11.74	2.08	3.52
2026	11.71	2.08	3.49
2027	11.69	2.07	3.46
2028	11.66	2.07	3.43
2029	11.63	2.06	3.40
2030	11.60	2.06	3.37
Average ('22-'30)	11.71	2.08	3.49
CAGR	-0.2%	-0.2%	-0.9%

Source: Wallace et al. 2017m, Korsmo et al. 2019, Derbyshire et al. 2020. Centers for Disease Control and Prevention, US Census, and Frost & Sullivan analysis

Chart 34. Target Population Size and Prevalence of Early Childhood Cognitive Development Disorder, 3 to 8 years old, United States, 2021-2030



	'21	'22	'23	'24	'25	'26	'27	'28	'29	'30
Children with Disorder	2.1	2.1	2.1	2.1	2.1	2.1	2.1	2.1	2.1	2.1
Heathy Children	9.7	9.7	9.7	9.7	9.7	9.6	9.6	9.6	9.6	9.5
All Children	11.9	11.8	11.8	11.8	11.7	11.7	11.7	11.7	11.6	11.6

Source: Wallace et al. 2017m, Korsmo et al. 2019, Derbyshire et al. 2020. Centers for Disease Control and Prevention, US Census, and Frost & Sullivan analysis

Early childhood cognitive development disorders include a wide set of neurocognitive disorders including autism, learning disorders, ADHD, fetal alcohol spectrum disorders, and language disorders [189,190]. There are over 2.1 million children ages 3 to 8 that have cognitive development disorders in the U.S., an event risk of 9.3% given a total population of 24.0 million children ages 3 to 8 years old [189,190]. It should be noted that there can be many factors that cause these disorders and may not necessarily be related to only maternal choline intake. In the next section, the scientific research that does exist exploring this association will be assessed in more detail.

Table 82. Population Health Care Costs Attributed to Early Childhood Cognitive Development Disorder from Inadequate Maternal Choline Intake, Children Aged 3 to 8, $USD Billion, United States, 2021-2030

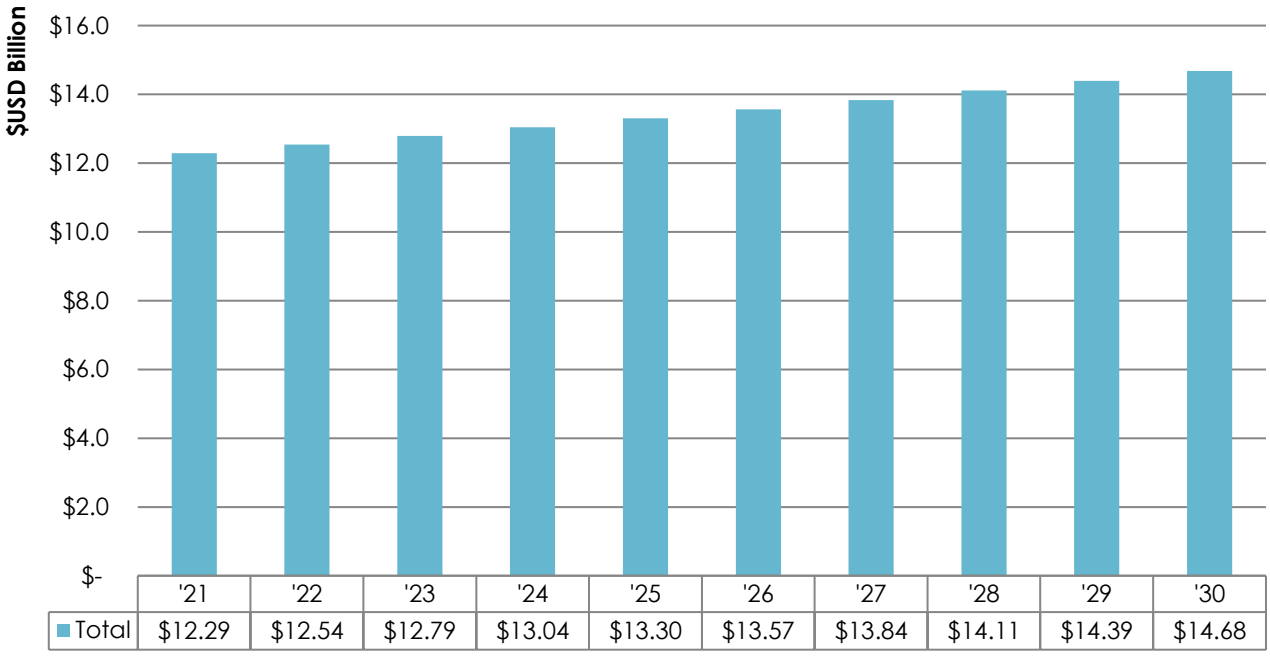
Year	Inadequate Maternal Choline Intake & Childhood Cognitive Development, Cost per Person Case, $ per Child	Inadequate Maternal Choline Intake & Childhood Cognitive Development, Total Cost ($ billion)
2021	$5,844	$12.293
2022	$5,974	$12.538
2023	$6,108	$12.787
2024	$6,244	$13.042
2025	$6,384	$13.302
2026	$6,526	$13.566
2027	$6,672	$13.836
2028	$6,821	$14.111
2029	$6,973	$14.392
2030	$7,129	$14.678
Average ('22-'30)	$6,537	$13.583
CAGR	2.23%	1.99%
Cumulative ('22-'30)		$122.251

Source: Suryavanshi et al. 2016, Davis et al. 2014, Centers for Disease Control and Prevention, US Census, and Frost & Sullivan analysis

These children will typically require more resources to manage and overcome the challenges associated with disorders compared to children without the disorder. Specifically, direct medical expenditures related to Early Childhood Cognitive Development Disorders for all children ages 5 to 17 was found to be $2,192 per child in 2011, an equivalent of approximately $2,700 today [191]. More recently, researchers investigating the rate of change in childhood mental illness and

associated healthcare costs found that children with a mental disorder paid $5,061 more per capita compared to control cases, an equivalent of $5,844 per capita in 2021 dollars [192]. Using this more recent cost burden per capita estimate and given an expected compound annual population growth rate of 2.0% and an average rate of inflation rate of 2.7% during the forecast period of 2022 to 2030, it is expected that the total expected direct medical expenditures on all early childhood cognitive development disorder-related events for all children ages 3 to 8 will exceed $14.68 billion by 2030.

Chart 35. Total Population Health Care Costs Attributed to Early Childhood Cognitive Development Disorder from Inadequate Maternal Choline Intake, Children Aged 3 to 8, $USD Billion, United States, 2021-2030



	'21	'22	'23	'24	'25	'26	'27	'28	'29	'30
Total	$12.29	$12.54	$12.79	$13.04	$13.30	$13.57	$13.84	$14.11	$14.39	$14.68

Source: Suryavanshi et al. 2016, Davis et al. 2014, Wallace et al. 2017, Korsmo et al. 2019, Derbyshire et al. 2020. Centers for Disease Control and Prevention, US Census, and Frost & Sullivan analysis

As in any other case, prevention of an event is critical in lowering the demand for disease management services. One way to control the burden of early childhood cognitive development disorder costs is to minimize the number of costly events that are possible in a target at-risk population. An early childhood cognitive development disorder event is expected to be partially preventable, or its seriousness can be significantly reduced, because it is caused, in part, by the mother of the child's dietary habits. Accordingly, motivating mothers to adopt new dietary behaviors, including the use of specially formulated dietary supplements high in metabolizable choline ought to be considered.

In the following case study, it will be shown that addressing the inadequate maternal intake of choline with dietary supplement products are associated with positive effects on their child's

eventual cognitive performance of their child soon after birth. This in turn is expected to result in economic implications in terms of avoided medical costs by these families. Specifically, this chapter explores the possible health and economic effects of the child that could be derived from their mothers using choline dietary supplements during pregnancy. A description of the latest scientific literature that tests for and supports aforementioned claims will be provided as well as implications for US healthcare stakeholders in terms of number of potentially avoidable events given the use of choline supplements.

Regarding cost estimate forecasts, expected compound annual growth rates (CAGR) were derived from a historic assessment of population growth rates and price inflation growth. Specifically, health care costs per person are expected to grow at an average annual growth rate of 2.2% from 2022 to 2030 based on the observed average price inflationary growth rate over the last 10 years. Given current inflation rates, we consider this expected growth rate to be conservative. Also, this growth rate was applied for all procedures for all conditions assessed in this study. Growth in the targeted population was expected to occur at the average annual growth rate of the population as a whole 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 were expected to grow at a compound annual growth rate of 2.2% per year, the same as price growth in general. The authors do not endorse the specific findings of any scientific study reviewed.

Table 83. Early Childhood Cognitive Development Disorder from Inadequate Maternal Choline Intake Cost Summary Statistics, 2021–2030

Metric	'21	CAGR ('21 - '30)	Average ('22 - '30)	Cumulative ('22 - '30)
Total child population, ages 3 to 8, million people	11.85 M	-0.2%	11.71 M	--
Total mother population, ages 13 to 44, million people	3.64 M	-0.9%	3.49 M	--
Population of children with Early Childhood Cognitive Development Disorder (people at high risk of experiencing an event), million people	2.10 M	-0.2%	2.08 M	--
Population of mothers with Inadequate Maternal Choline Intake, million people	3.33 M	-0.9%	3.20 M	--
Event rate—percent of the high-risk child population diagnosed with Early Childhood Cognitive Development Disorders, %	17.5%	0.0%	17.5%	--
Total cost of Early Childhood Cognitive Development Disorders, $USD per Case	$5,844	2.23%	$6,537	--
Total target population cost of Early Childhood Cognitive Development Disorders, $USD billion	$12.293 B	1.99%	$13.583 B	$122.251 B
Price inflation rate, %	6.95%	--	2.23%	

Source: Suryavanshi et al. 2016, Davis et al. 2014, Wallace et al. 2017, Korsmo et al. 2019, Derbyshire et al. 2020. Centers for Disease Control and Prevention, US Census, and Frost & Sullivan analysis

Choline

Literature Review

As indicated in the prior section, there is a strong need to increase awareness among health professionals and consumers regarding potential suboptimal intakes of choline in the United States, as well as the critical role that choline plays in mental health maintenance throughout the lifespan. Choline is an essential nutrient that the body requires in order to synthesize phosphatidylcholine and sphingomyelin, two major phospholipids vital for cell membranes [10]. All plant and animal cells require choline to preserve their structural integrity and choline is required to produce acetylcholine, an important neurotransmitter for mood, memory, muscle control, and other brain and nervous system functions [10]. Choline also plays an important role in modulating gene expression, cell membrane signaling, lipid transport and metabolism, and early brain development.

The U.S. Food and Drug Administration (FDA) developed daily values (DVs) to help consumers compare the nutrient contents of foods and dietary supplements within the context of a total diet. The DV for choline is 550 mg for adults and children aged 4 years and older [194]. The FDA does not need food labels to list choline content unless choline has been added to the food. Foods providing 20% or more of the DV are considered to be high sources of a nutrient; however, foods providing lower percentages of the DV also contribute to a healthful diet. Most people in the U.S. consume less than the AI for choline. An analysis of data from the 2013–2014 National Health and Nutrition Examination Survey (NHANES) found that the average daily choline intake from foods and beverages among children and teens is 256 mg for ages 2–19 [194]. In adults, the average daily choline intake from foods and beverages is 402 mg in men and 278 mg in women. Intakes from supplements contribute a very small amount to total choline intakes [194].

To infer the expected efficacy of using choline on the occurrence of an early childhood cognitive development disorder event, a literature review was conducted in March 2022 that focused on published studies that tested for and quantified the effect of choline supplementation on the incidence of early childhood cognitive development disorder events. The goal of this assessment was to collect a sample of studies that represented the state of all scientific literature on choline supplementation. In addition, studies selected for analysis must have tested for a direct causal relationship between the intake of a choline dietary supplement regimen and the relative risk of an early childhood cognitive development disorder event. It was preferred that the selected studies were similar in study protocol in an attempt to control likely variances, though this is not always possible due to the nature of it being a young body of research. Studies were not selected on the basis of the magnitude, direction, or statistical significance of the reported findings.

Forty-six (46) studies were found in a PubMed search based on the use of "choline" and "intake" and "maternal" or "prenatal"; and "cognitive development" and their respective synonyms as filtering keywords. The search was conducted between March 1 and March 31, 2022. Only five (5) relevant studies were identified as representative of the choline literature as it related to this topic and were used to deduce the estimated efficacy of high intake of choline of during pregnancy on reducing early childhood cognitive development disorder event risk of the child. Table 84 provides a description of the included studies in the final meta-analysis below.

Table 84. Choline Literature Review: Description of the Qualified Studies

Ref.	Author	Year	Sample Size	Study Duration	Cognitive Performance Test
199	Bahnfleth	2022	20	84 months	Sustained Attention Score
198	Caudill	2018	24	13 months	Saccade reaction time
202	Ross	2016	49	40 months	Performance on Child Behavior Checklist
200	Cheatham	2012	99	12 months	Global Development Index
203	Wu	2021	154	2nd T. n = 154 mother-infant pairs.	Early cognitive development

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

In 2018, researchers evaluated that the maternal choline supplementation during the third trimester of pregnancy improves infant information processing speed [195]. The primary outcome was the mean saccade reaction time for the stimulus-guided fixation shifts. The secondary outcome was the number of predictive saccades. Both outcomes were measured at the age of 4, 7, 10, and 13 months and were computed separately for fixation shifts to unpredictable stimuli during the baseline sequence and for fixation shifts during the post baseline alternating sequence [195]. The researchers concluded that choline supplementation of the diet at a level exceeding the current AI among women in their third trimester of pregnancy improved infant processing speed relative to maternal consumption of the AI [195]. The finding suggests that the current AI level for choline during pregnancy may need to be increased for improved offspring cognitive functioning.

In 2022, researchers focused on how prenatal choline supplementation improved their child's sustained attention [196]. Of the 4,320 trials administered, a valid response was recorded on 4,315 trials; five trials were excluded due to technical problems. On average, children correctly identified the presence of the signal on 78% (Median: 83%, interquartile range [IQR]: 67% - 92%) of all signal trials and correctly noted the absence of a signal on 78% (Median: 82%, IQR: 71% – 91%) of non-signal trials [196]. Across all children, the 17 milliseconds signal was more difficult to detect than either the 29 milliseconds or 50 milliseconds signals [196]. Specifically, children averaged 70% hits on 17 milliseconds trials, compared to 86% hits for the 29 milliseconds and 85% for 50 milliseconds trials (17 milliseconds vs. average of 29 and 50 milliseconds: t (114) = 7.69, 95% CI [-0.20, -0.12], P < .001). A vigilance decrement for the hit percentage was also seen in the group as a whole, as evidenced by a lower hit rate during the third trial block (76%) compared to the first trial block (84%; t (38) = 2.51, 95% CI [0.02, 0.15], P = .02) [199]. The overall omission rate was very low (Median: 3.7%, IQR: 2.1% – 13.4%) and did not change from block 1 to block 3 (t (86.94) = 0.43, 95% CI [-0.67, 2.07], P = .67), indicating that children responded consistently throughout the task. Results are next presented for each endpoint in models that include choline treatment group and planned tests of hypotheses concerning interactions between choline group, signal duration, and trial block.

In 2012, researchers evaluated that phosphatidylcholine supplementation in pregnant women consuming moderate-choline diets does not enhance infant cognitive function [197]. In this double-blind, randomized controlled trial, 140 pregnant women were randomly assigned to receive supplemental phosphatidylcholine (750 mg) or a placebo (corn oil) from 18-week gestation through 90-day post-partum [197]. Their infants (n = 99) were tested for short-term visuospatial memory, long-term episodic memory, language development, and global development at 10 and 12 months of age [197]. The researchers found that phosphatidylcholine supplementation of pregnant women eating diets containing moderate amounts of choline did not enhance their infants' brain function. It is possible that a longer follow-up period would reveal late-emerging effects. Moreover, future studies should determine whether supplementing mothers eating diets much lower in choline content, such as those consumed in several low-income countries would enhance infant brain development. Moreover, in 2013, researchers studied the choline intake during pregnancy and child cognition at age 7 years [198]. The researchers found a stronger association of child memory with second-trimester choline intake than with first-trimester intake [198]. This finding may suggest a stronger effect of choline on brain formation in mid-gestation than early in pregnancy. And in 2016, researchers have also evaluated the perinatal phosphatidylcholine supplementation and early childhood behavior problems with an aim to understand the evidence for CHRNA7 moderation [199]. The researchers reported that newborns in the phosphatidylcholine treatment group have increased suppression of the cerebral evoked response to repeated auditory stimuli [199]. They further reported the parental assessments of the children's behavior at 40 months of age, using the Child Behavior Checklist.

A study from 2012 was conducted to explore the relationship between second trimester maternal plasma choline and betaine levels and measures of early cognitive development in their infants [200]. This was a study of healthy pregnant women and their full-term, single birth infants [200]. Maternal blood was collected at 16 and 36 weeks of gestation and infant neurodevelopment was assessed at 18 months of age for 154 mother-infant pairs. Maternal plasma choline, betaine, dimethylglycine, methionine, homocysteine, cysteine, total B12, holotranscobalamin and folate were quantified [200]. Infant neurodevelopment was evaluated using the Bayley Scales of Infant Development-III [200]. The study found that the maternal plasma free choline at 16- and 36-week gestation was median (interquartile range) 6.70 (5.78-8.03) and 9.40 (8.10-11.3) µmol/L, respectively [203]. Estimated choline intakes were (mean ± SD) 383 ± 98.6 mg/day, and lower than the recommended 450 mg/day. Betaine intakes were 142 ± 70.2 mg/day. Significant positive associations were found between infant cognitive test scores and maternal plasma free choline (B=6.054, SE=2.283, p=0.009) and betaine (B=7.350, SE=1.933, p=0.0002) at 16 weeks of gestation [200].

Other studies were found that indirectly support the relationship between maternal use of choline supplements and possible associations with childhood cognitive development though they were not used in the final meta-analysis due to differences in study design. In 2016, researchers investigated the association between betaine and choline intake among adolescents and academic achievement [202]. The researchers found that plasma choline levels were significantly and positively associated with academic achievement with all other factors being equal (such as paternal education and income, maternal education and income, smoking, school) and of folate intake (P = 0.009) [202]. Thus, this study showed a direct link between choline plasma levels and performance, though more research is required to confirm an association between choline intake and academic performance. In another study published in 2020, researchers investigated choline plasma levels among mothers given various levels of choline supplement use [203]. The researchers found that prenatal use of choline supplements significantly improved choline metabolism and greater plasma enrichment levels of choline in the placenta and umbilical cord [203].

To deduce the effect of using choline on the occurrence of an early childhood cognitive development disorder event, a random-effects meta-analysis model was developed based on the systematic review process developed by DerSimonian and Laird (1986) which is a common approach for deducing the true treatment effect from a set of clinical research citations that varies by sample size, methodologies and study protocols, and patient population dynamics [5, 37]. 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 [5, 37]. It should be noted that only five studies were discovered for this

assessment and each study did still vary quite considerably in terms of study protocol and research design, including study duration and study quality. Hence, the aggregated results reported below should be taken as only an indication of the possible association and that further experiments testing this association needs to be produced and replicated in order to build confidence of the expected results.

After application of the random-effects meta-analysis model to the qualified set of clinical studies described in detail above, it is expected that the weighted standard mean difference (WSMD) of an early childhood cognitive development disorder event, given the preventive use of choline supplements by mothers during the child's gestation, or the reported Cohen's d score, is 0.226 (95% CI: 0.059 – 0.393) after controlling for variance caused by study sample size, research protocols, and patient population differences within each study and among all studies.

A Cohen's d effect size score is a way to standardize similar types of tests into one overarching expected effect size [201]. All of the different types of reported outcomes used by the researchers in the eligible studies measured the mean difference in cognitive performance of the infant and/or child of mothers who were with and without adequate choline during pregnancy, independent of the cognitive performance test used. It can be shown that an effect size of 0.226 means that approximately 90.8% (95% CI: 84.5% - 97.6%) of the population of children with early childhood cognitive development disorder due to the inadequate of maternal choline during gestation perform similarly to the population of children without an early childhood cognitive development disorder and that 9.2% (95% CI: 2.4% – 15.5%) of the healthy child group's cognitive performance is equal to or better than the best performing child in the control group [201]. Thus, 9.2% of children with mothers who had adequate intake of choline during pregnancy had better cognitive performance than the best-off child in the childhood cognitive development disorder due to the inadequate of maternal choline during gestation group.

Given an early childhood cognitive development disorder event risk of 17.8% among children ages 3 to 8, the number of mothers that would need to use a choline supplement to avoid one early childhood cognitive development disorder from developing among the target population of children is approximately 61 (95% CI: 36-235) people. In other words, if approximately 61 mothers with inadequate of choline were to have used choline supplements at recommended intake levels for healthy child development; one child will avoid an early childhood cognitive development disorder. Given an NNT of 61 people, the number of potential avoided events among all children aged 3 to 8 diagnosed with an early childhood cognitive development disorder could be an estimated 59,108 avoided events in 2022 and is expected to be an average of 57,128 events per year from 2022 to 2030 given current population and disease risk growth expectations. Table 85 describes the empirical results of the included studies in the final systematic review and Table 86 reports the

aggregated expected effect size of choline use on early childhood cognitive development disorder risk.

Table 85. Choline Literature Review: Summary of Study Findings

Author	Total sample (N)	Standardized Mean Difference (Cohen's d, Improvement Effect Size)	95% Low	95% High	Study weight (based on random effects model)
Bahnfleth	20	0.8385	0.3913	1.2857	5.8%
Caudill	24	0.4255	0.0245	0.8246	6.9%
Ross	49	0.4115	0.1258	0.6972	14.2
Cheatham	99	0.0163	0.0134	0.0192	28.6%
Wu	154	0.1914	0.0302	0.3526	44.5%

Source: Frost & Sullivan analysis

Table 86. Expected Efficacy of Supplement Use Based on Literature Review, Choline

Metric	Measure
Standardized Weighted Mean Difference (weighted for intra-study variance) (WMD)	0.226 (95% CI: 0.059-0.393)
% Overlap of Same Level of Cognitive Performance distribution between the Adequate Intake Group and Inadequate Intake Group, %	90.8% (95% CI: 84.5%-97.6%)
% of Adequate Intake Group who Performed better than the Inadequate Intake Group with respect to relative cognitive performance, %	9.2% (95% CI: 2.4%-15.5%)
Number of people needed to treat to avoid one Early Childhood Cognitive Development Disorder event (NNT), # of mothers using choline	61 (95% CI: 36-235)
Estimated number of events that could have been avoided if the entire target population used choline in 2022	59,108
Average number of events avoided annually if the entire target population used choline, 2022-2030	57,128

Source: Frost & Sullivan analysis

Economic Implications

Once the expected effect size was determined from the literature, the potential cost savings derived from choline dietary supplement usage at preventive daily intake levels among the target market of expectant mothers was calculated and compared with zero usage [22]. The calculation of total cost savings is straightforward – the 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 cost of dietary supplement use by the entire target high-risk cohort equals potential net cost savings [22].

Accordingly, if the potential net cost savings are positive, then the use of choline supplement regimen ought to be considered as a means to support expectant mothers and their children [155]. Of course, the prior cost-benefit analysis approach makes the assumption that in the supplementation scenario, the entire population of the target high-risk cohort used the given dietary supplements at protective intake levels, and this was compared to zero use in that population segment. In other words, the calculated net savings is actually the maximum potential net savings theoretically achievable. However, because it is likely that a part of the target cohort of mothers are already regular users of choline supplements and would already be realizing its risk-reducing benefits, while the remainder of the potential regular users has yet to realize the potential preventive benefits from regular use. Because avoided expenditures and net cost savings are a 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 by the number of current users. These yet-to-be-realized adjustments are also calculated below.

Given the risk reducing effect of the maternal use of choline supplements during pregnancy on early childhood cognitive development disorders, the expected reduction in expenditures in 2022 attributed to avoided Early Childhood Cognitive Development Disorder events would have been $353 million in 2022 given an average difference in health care costs associated with early childhood cognitive development disorder. Given current population growth, risk growth and price inflationary factors, the expected cost savings derived from avoided early childhood cognitive development disorder events given maternal use of choline at protective intake levels during pregnancy is $373 million per year in total savings from 2022 to 2030.

In order to ensure that all cost considerations are taken into account, the cost of using dietary supplements ought to be included in the final accounting. Based on the review of the best-selling retail products currently sold through online sales channels, the median cost of a daily dose of choline is approximately $0.24 per day. Given this daily cost requirement, the median expected total cost of choline dietary supplementation for all U.S. mothers aged 13 to 44 during 9 months of pregnancy would be $72.71 per person per year or $253 million per year for the total population over the period 2022 to 2030. Table 87 provides a summary of the cost of dietary supplementation with choline of the entire target population.

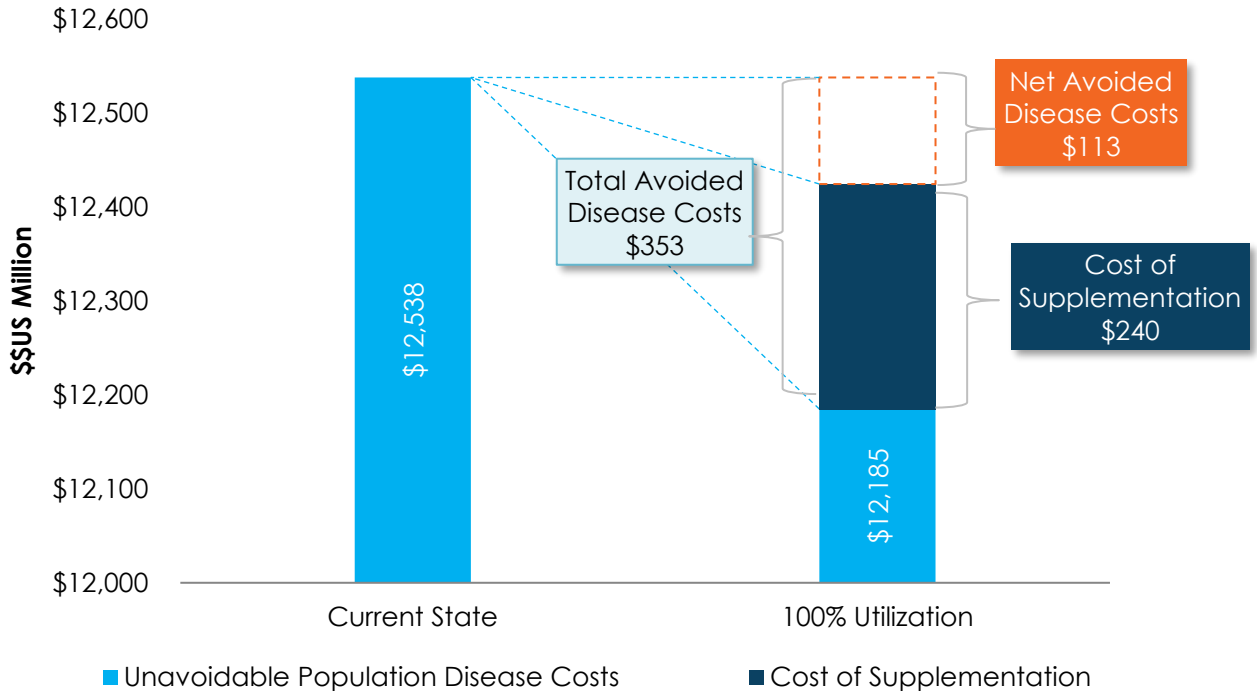
Table 87. Choline Cost Analysis: Summary Results—Cost of Dietary Supplementation of the Target Population*, 2022-2030

Metric	Measure
Median daily cost per person of Choline supplementation at protective daily intake levels, 2022	$0.24
Expected daily median cost per person of Choline supplementation at protective daily intake levels, 2022-2030	$0.27
Median cost per mother of Choline supplementation at protective daily intake levels, 9-month duration, 2022	$66.41
Expected annual median cost per mother of Choline supplementation at protective daily intake levels, 9-month duration, 2022-2030	$72.71
Total target population cost of Choline supplementation at protective daily intake levels, 2022	$0.240 B
Total target population cost of Choline supplementation at protective daily intake levels, 2022-2030	$0.253 B

Note: M indicates million. B indicates billion. Source: Frost & Sullivan analysis

Given the incurred cost of choline dietary supplementation, the net cost savings expected from reduced health care-attributed expenditures in 2022 from avoided early childhood cognitive development disorder events would have been $113 million in 2022 or $120 million per year in net savings during the period 2022 to 2030, or over $1.0 billion in cumulative savings in added health care costs associated with early childhood cognitive performance disorders. Table 88 reports the economic implications of the systematic review findings of the beneficial use of choline supplements.

Chart 36. Choline Cost Analysis: Health Care Cost Savings from the Use of Health Supplement, 2022 Scenario Analysis



Source: Frost & Sullivan analysis

Table 88. Choline Cost Analysis: Summary Results—Avoided Added Medical Expenditures due to Dietary Supplement Intervention, 2022-2030

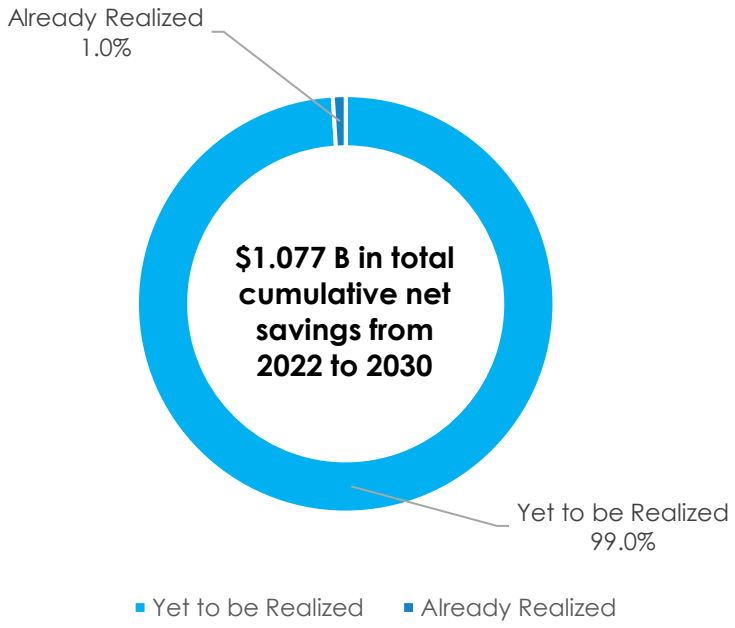
Metric	Measure
Avoided Early Childhood Cognitive Development Disorders-attributed care expenditures given mother Choline supplement intervention per year, 2022	$353 M
Average avoided Early Childhood Cognitive Development Disorders-attributed hospital utilization expenditures given Choline supplement intervention per year, 2022-2030	$373 M
Net avoided Early Childhood Cognitive Development Disorders-attributed hospital utilization expenditures given Choline supplement intervention per year, 2022 (includes cost of supplementation)	$113 M
Net average avoided Early Childhood Cognitive Development Disorders-attributed hospital utilization expenditures given Choline supplement intervention per year, 2022-2030 (includes cost of supplementation)	$120 M
Net benefit cost ratio, $ Savings per one dollar spent on dietary supplement	$1.46
Cumulative net target avoided costs, 2022-2030 (NET BENEFITS) ($ billion)	$1.077 B

Note: M indicates million. B indicates billion. Source: Frost & Sullivan analysis

The above cost savings results are the maximum savings potential that is obtainable if everyone in the target population (all mothers aged 13 to 44) had not used this product prior to the base year of analysis (e.g., 2022) and then 100% of the population adopted the choline regimen in the same year and gained all potential benefits. This assumption was made in order to calculate per capita net benefits which in turn can be used to calculate the net avoided cost savings for the subset of the population yet to use choline.

Today, the use of choline supplements is very low. According to the 2021 Council for Responsible Nutrition Consumer Survey on Dietary Supplements conducted by Ipsos Public Affairs, only 1% of U.S. female dietary supplement users aged 18 and over actually use choline dietary supplements [21]. This implies that effectively all potentially avoidable costs will go unrealized in 2022. If utilization rates go unchanged, a cumulative cost savings opportunity of $1.067 billion from 2022 to 2030 could be lost because of underutilization of choline dietary supplements. In summary, it has been demonstrated that adequate maternal intake of choline with dietary supplement products can lead to positive health and economic benefits from supporting their child's neurocognitive development in the future.

Chart 37. Choline Cost Analysis: Summary Results— Cumulative Net Cost Savings Yet to be Realized due to Avoided Hospital Utilization Expenditures through Dietary Supplement Intervention, 2022-2030



Note: M indicates million. B indicates billion. Source: Frost & Sullivan analysis

Table 89. Choline Cost Analysis: Summary Results — Net Cost Savings Yet to be Realized due to Avoided Hospital Utilization Expenditures through Dietary Supplement Intervention, 2022-2030

Metric	Measure
Net avoided Early Childhood Cognitive Development Disorders-attributed care expenditures given mother Choline supplement intervention yet to be realized per year, 2022	$112 M
Net average Early Childhood Cognitive Development Disorders-attributed care expenditures given mother Choline supplement intervention yet to be realized per year, 2022-2030	$119 M
Cumulative net target avoided costs yet realized, 2022-2030 (NET BENEFITS) ($ billion)	$1.067 B

Note: M indicates million. B indicates billion. Source: Frost & Sullivan analysis

Detailed Results

Table 90. Choline Cost Analysis: Detailed Results—Cost of Dietary Supplementation of the Target Population, 2022-2030

Year	Choline, Daily Cost of Supplementation ($ per day)	Choline, Annual Cost of Supplementation ($ per year)	Choline, Population Cost of Supplementation ($ billion)
2021	$0.23	$64.27	$0.234
2022	$0.24	$66.41	$0.240
2023	$0.25	$67.89	$0.243
2024	$0.25	$69.60	$0.247
2025	$0.26	$70.96	$0.250
2026	$0.26	$72.54	$0.253
2027	$0.27	$74.16	$0.256
2028	$0.28	$76.03	$0.261
2029	$0.28	$77.51	$0.263
2030	$0.29	$79.24	$0.267
Average ('22-'30)	$0.27	$72.71	$0.253
CAGR	2.4%	2.4%	1.5%
Cumulative ('22-'30)	--	--	$2.279

Source: Frost & Sullivan analysis

Table 91. Choline Cost Analysis: Detailed Results—Avoided Added Medical Expenditures due to Dietary Supplement Intervention, 2022-2030

Year	Choline, Maternal Deficiency and Childhood Cognitive Development, Number of Avoided Events if 100% Utilization by Target User Base (# of Avoided Event Cases)	Choline, Maternal Deficiency and Childhood Cognitive Development, Total Target Avoided Costs (BENEFITS) ($ billion)	Choline, Maternal Deficiency and Childhood Cognitive Development, Net Target Avoided Costs (NET BENEFITS) ($ billion)
2021	59,602	$0.348	$0.114
2022	59,108	$0.353	$0.113
2023	58,613	$0.358	$0.115
2024	58,118	$0.363	$0.116
2025	57,623	$0.368	$0.118
2026	57,128	$0.373	$0.120
2027	56,633	$0.378	$0.121
2028	56,138	$0.383	$0.122
2029	55,643	$0.388	$0.125
2030	55,148	$0.393	$0.126
Average ('22-'30)	57,128	$0.373	$0.120
CAGR	-0.9%	1.4%	1.1%
Cumulative ('22-'30)	514,151	$3.357	$1.077

Source: Frost & Sullivan analysis

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