

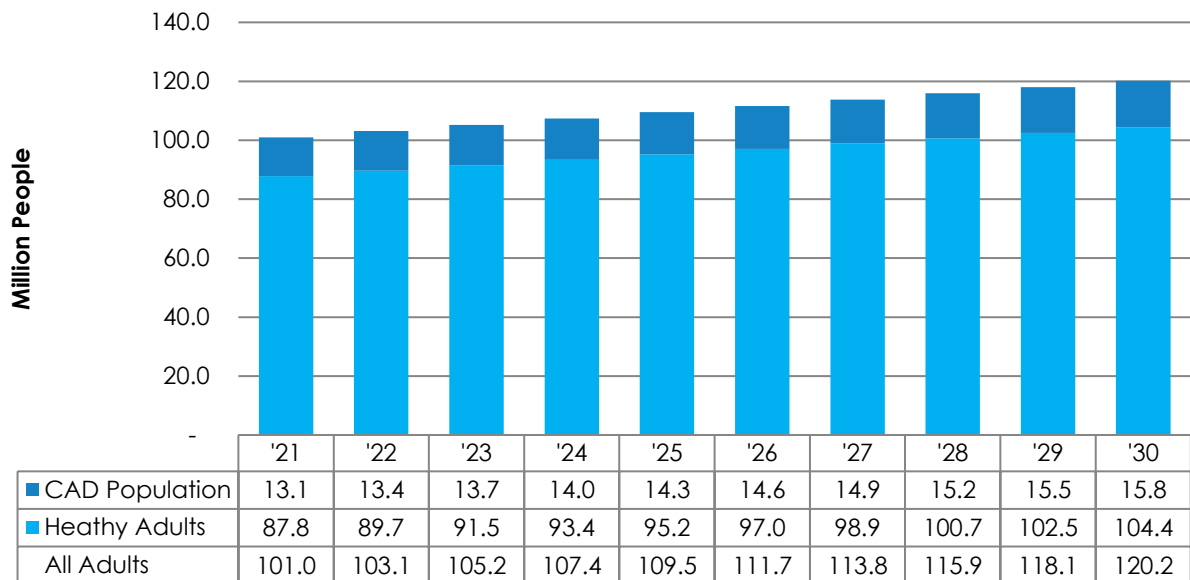
THE COST EFFECTIVENESS OF OMEGA-3, MAGNESIUM, SOLUBLE FIBER, AND VITAMIN K2 DIETARY SUPPLEMENTATION FOR MANAGING THE RISK OF CORONARY ARTERY DISEASE OUTCOMES

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



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

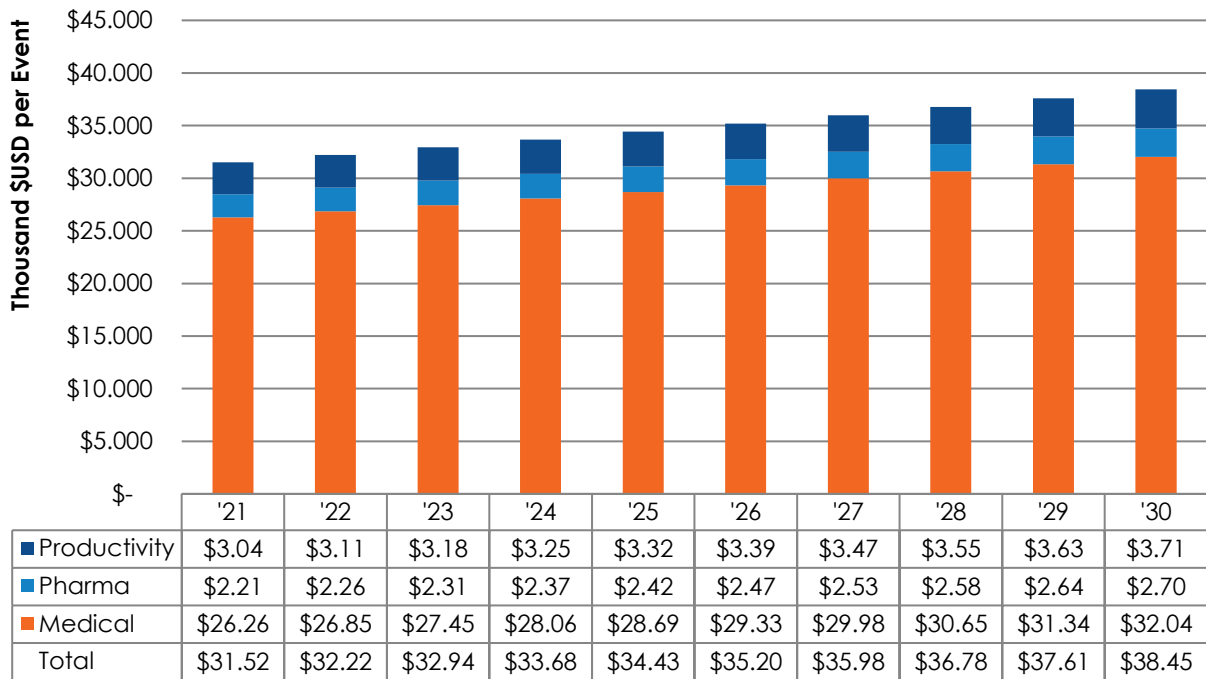
Year	Total Population, age 55 and older (million people)	Population of people experiencing CAD-attributed inpatient medical service or emergency room visits event, age 55 and older (million people)
2021	100.97	13.12
2022	103.11	13.43
2023	105.25	13.73
2024	107.38	14.03
2025	109.52	14.33
2026	111.66	14.63
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.

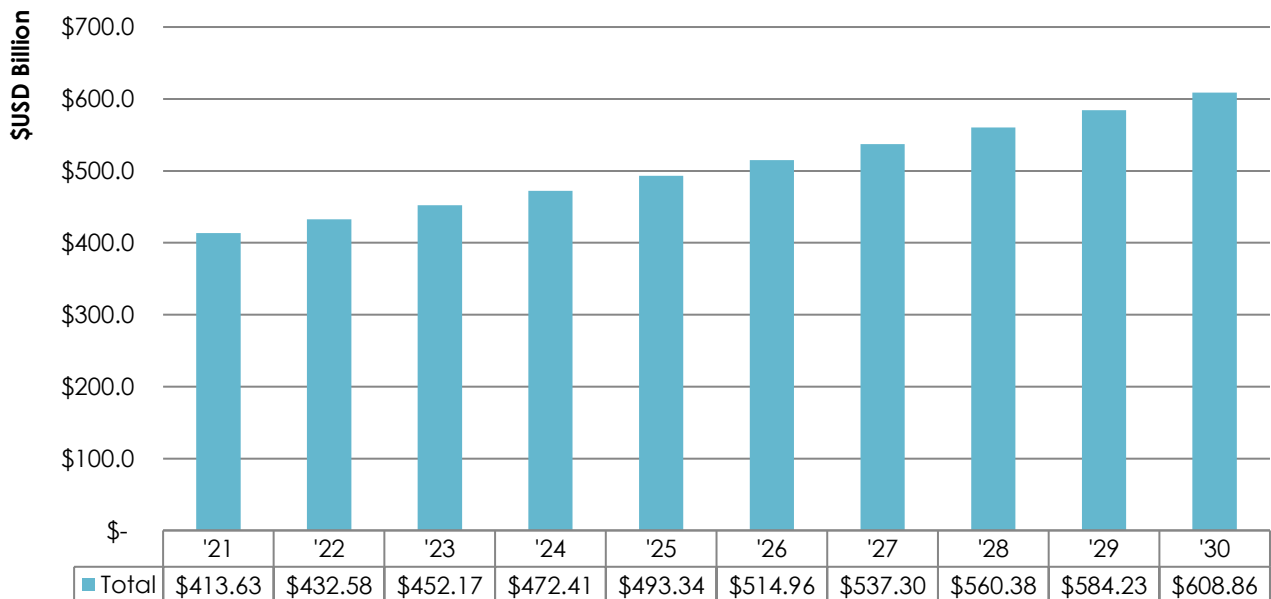
Given an expected compound annual population growth rate of 2.0% and an average inflation rate of 2.7% during the forecast period of 2022 to 2030, it is expected that the total expected direct medical expenditures on all CAD-related events for all U.S. adults aged 55 and older will exceed \$608.9 billion 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



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



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

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:

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

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 $\delta = 0.14$ 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

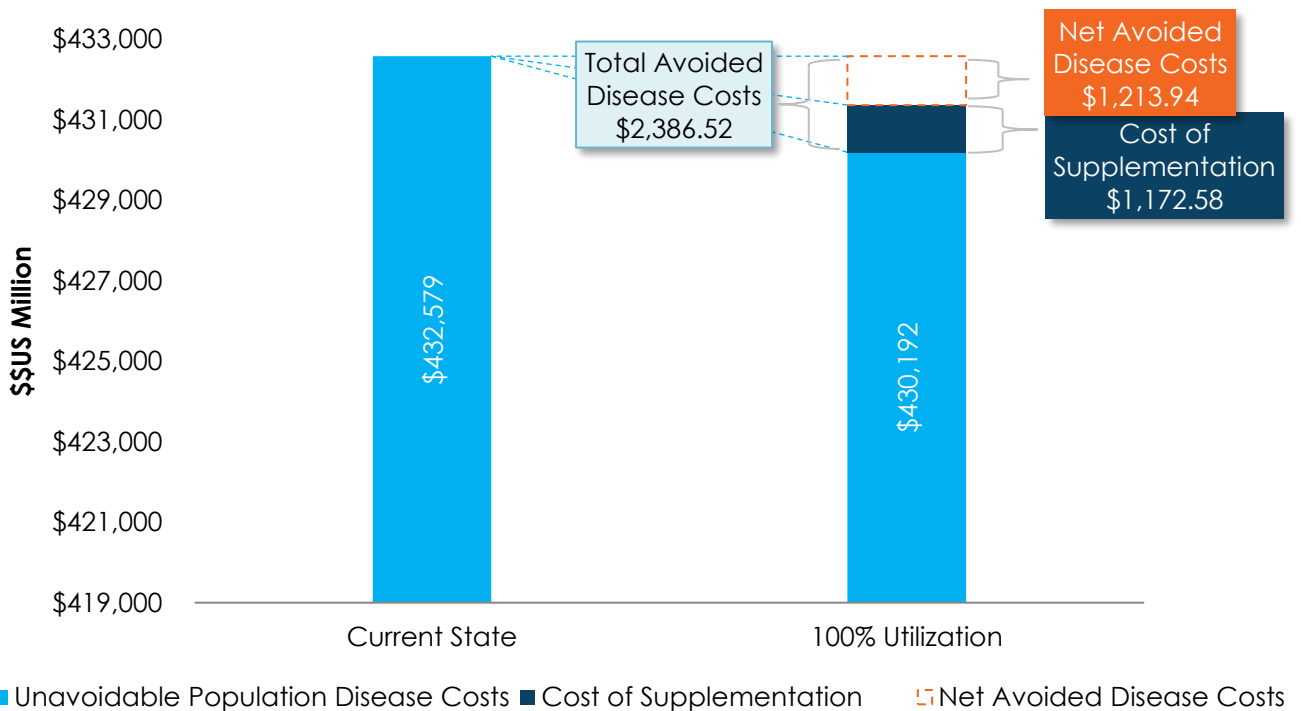
Based on the incurred cost of Soluble Fiber dietary supplementation, the net cost savings expected from reduced health care-attributed expenditures in 2022 derived from avoided CAD-attributed events would have been \$1.21 billion in 2022 or \$1.47 billion per year in net savings and \$13.23 billion in 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



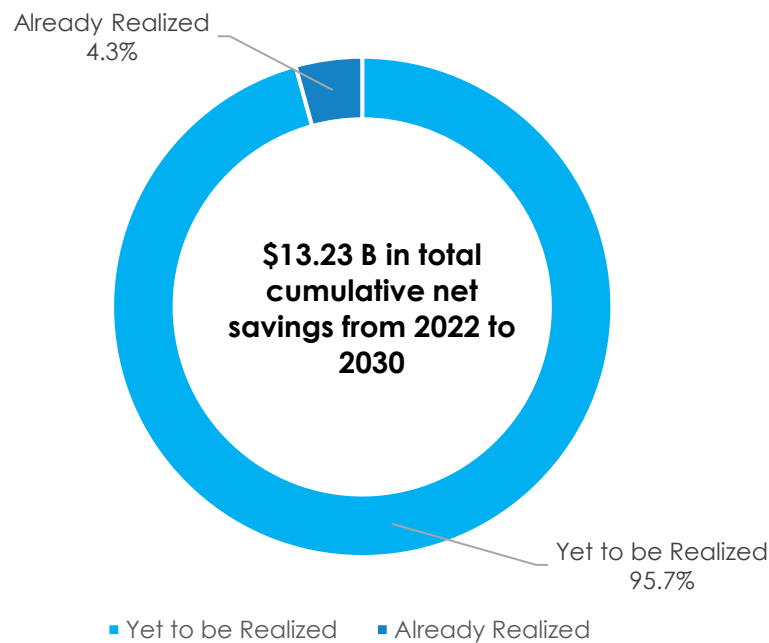
Note: B indicates billion. Source: Frost & Sullivan analysis

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 to 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.

