

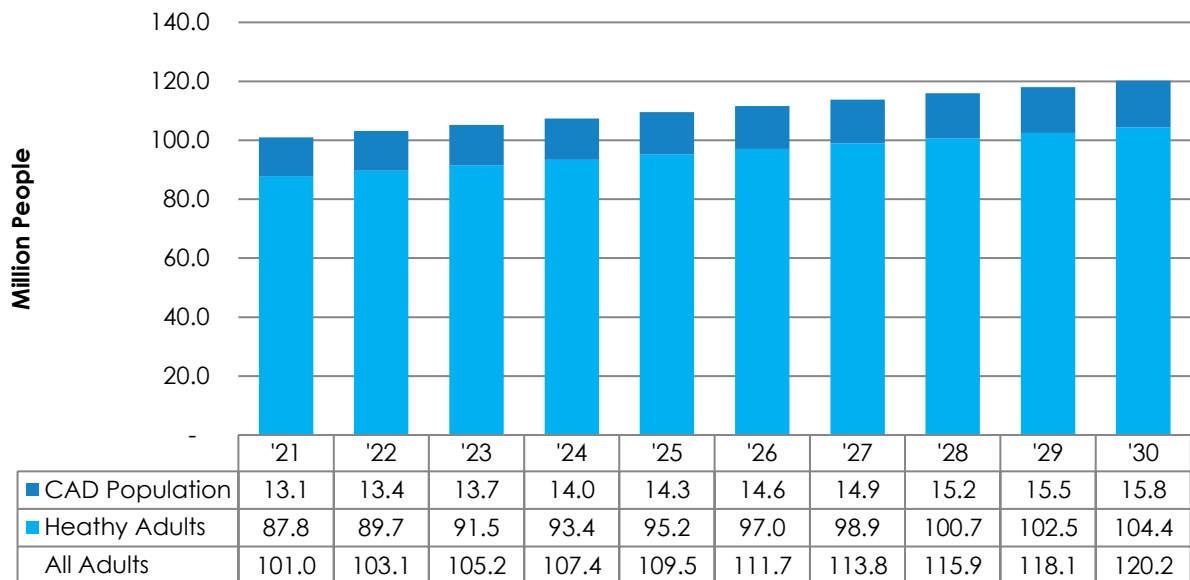
THE COST EFFECTIVENESS OF OMEGA-3, MAGNESIUM, SOLUBLE FIBER, AND VITAMIN K2 DIETARY SUPPLEMENTATION FOR MANAGING THE RISK OF CORONARY ARTERY DISEASE OUTCOMES

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

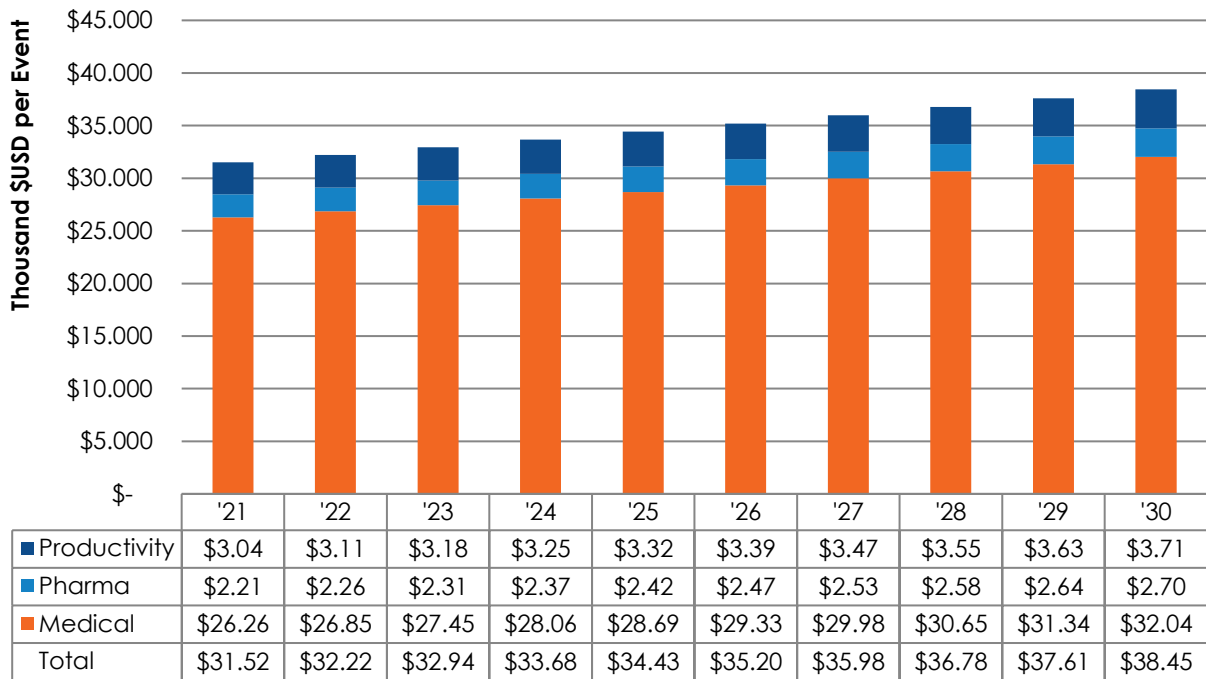
Year	Total Population, age 55 and older (million people)	Population of people experiencing CAD-attributed inpatient medical service or emergency room visits event, age 55 and older (million people)
2021	100.97	13.12
2022	103.11	13.43
2023	105.25	13.73
2024	107.38	14.03
2025	109.52	14.33
2026	111.66	14.63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

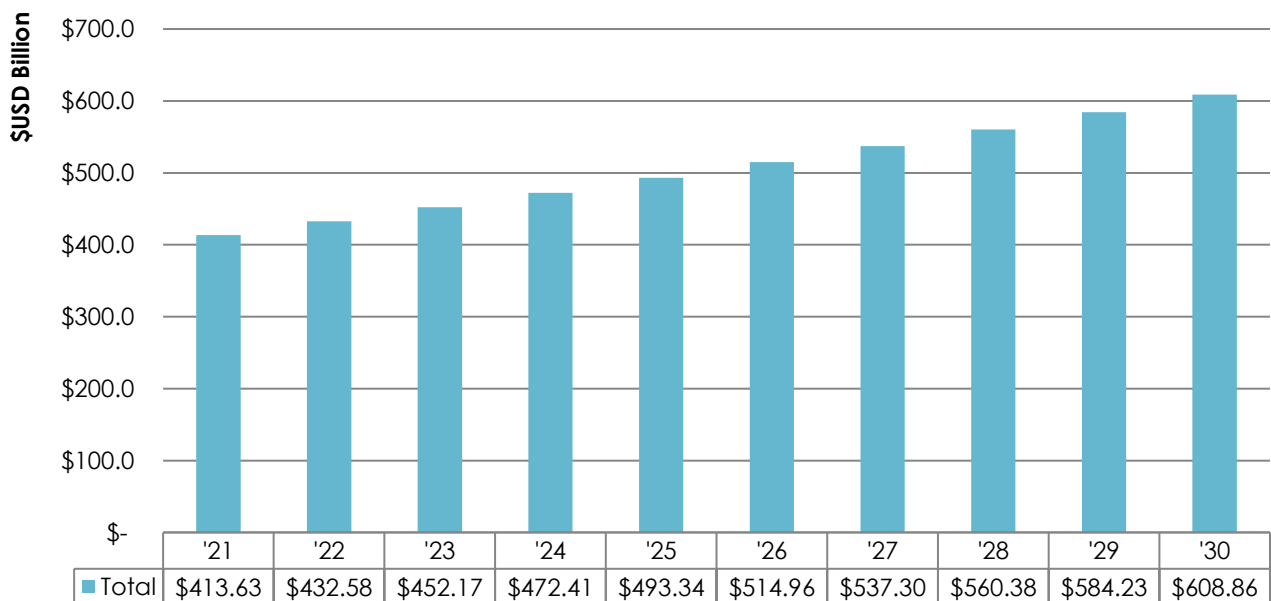
Given an expected compound annual population growth rate of 2.0% and an average inflation rate of 2.7% during the forecast period of 2022 to 2030, it is expected that the total expected direct medical expenditures on all CAD-related events for all U.S. adults aged 55 and older will exceed \$608.9 billion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

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 ($5.3\% = 6.0\% \times 1.78 \text{ mm Hg} / 2.00 \text{ mm Hg}$).

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

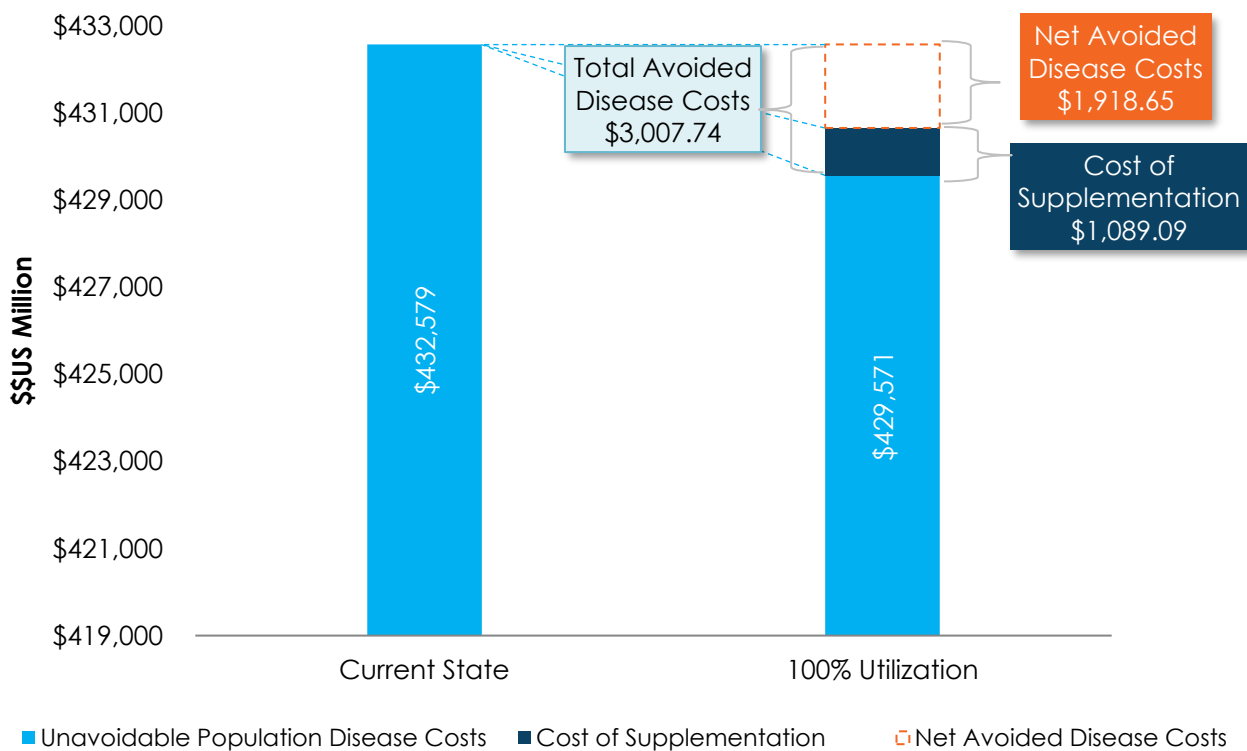
turn can be used to calculate the net potentially avoidable costs for the subset of the population yet to use magnesium.

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

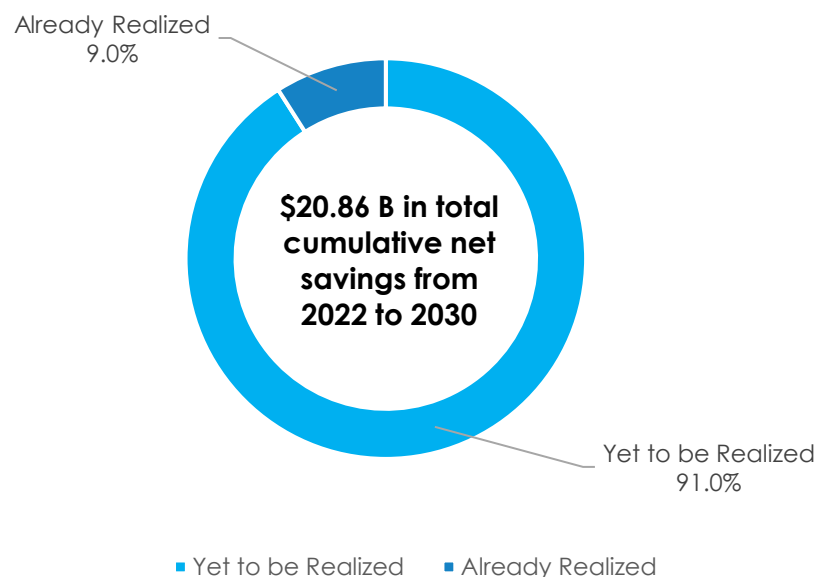


Note: B indicates billion. Source: Frost & Sullivan analysis

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.

