

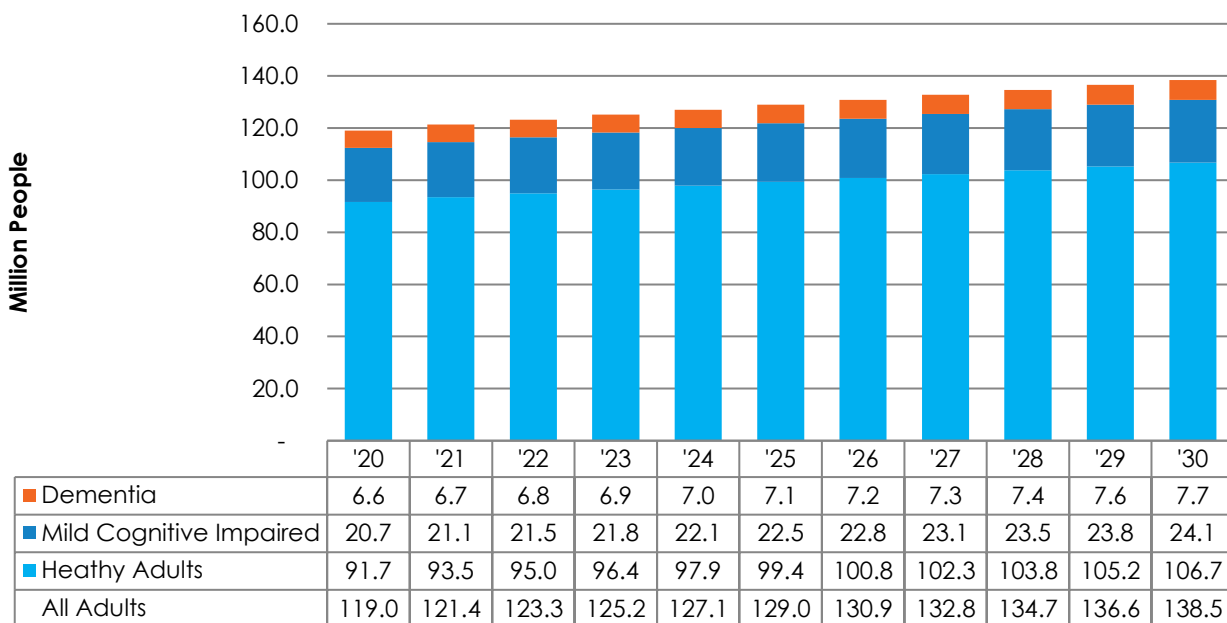
HEALTHCARE COST SAVINGS DERIVED FROM SLOWING COGNITIVE DECLINE WITH THE USE OF B VITAMINS

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



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%

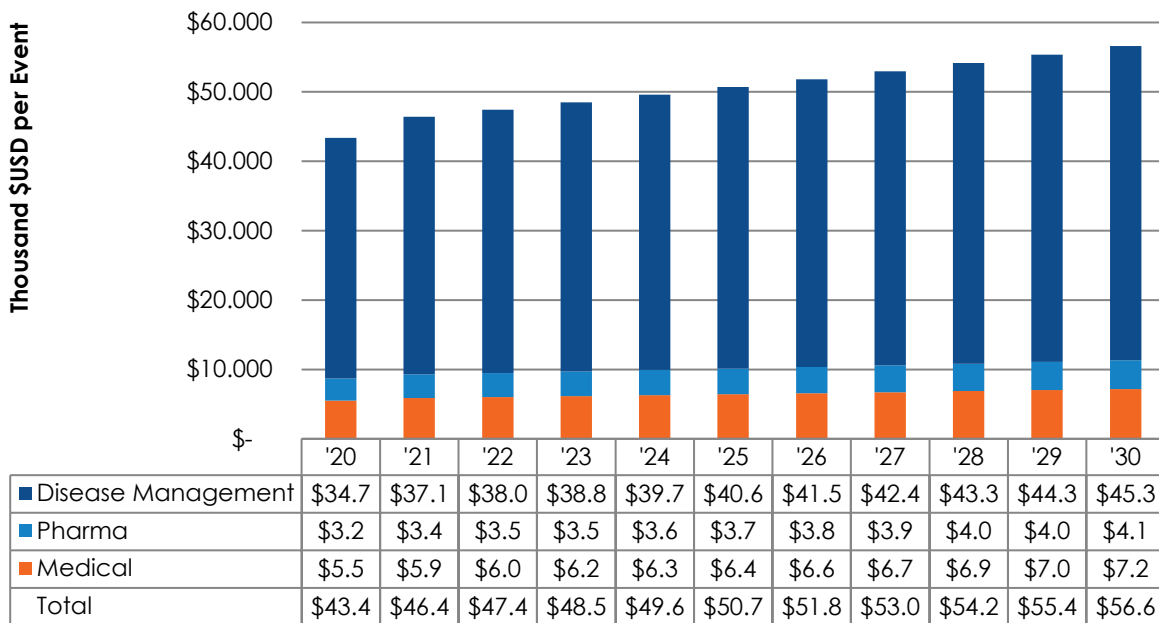
Source: Mayo Clinic, Hale et al. 2020, Alzheimer's Association (2022), US Census, and Frost & Sullivan analysis

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



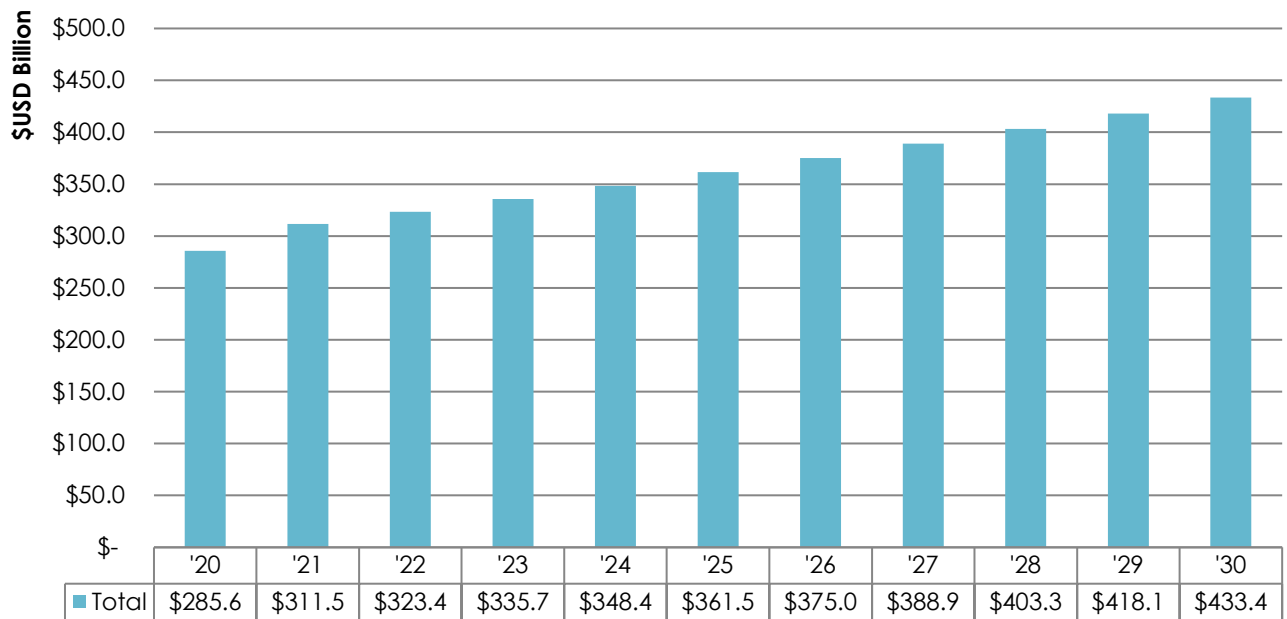
Source: Mayo Clinic, Hale et al. 2020, Alzheimer’s Association (2022), US Census, and Frost & Sullivan analysis

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



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.

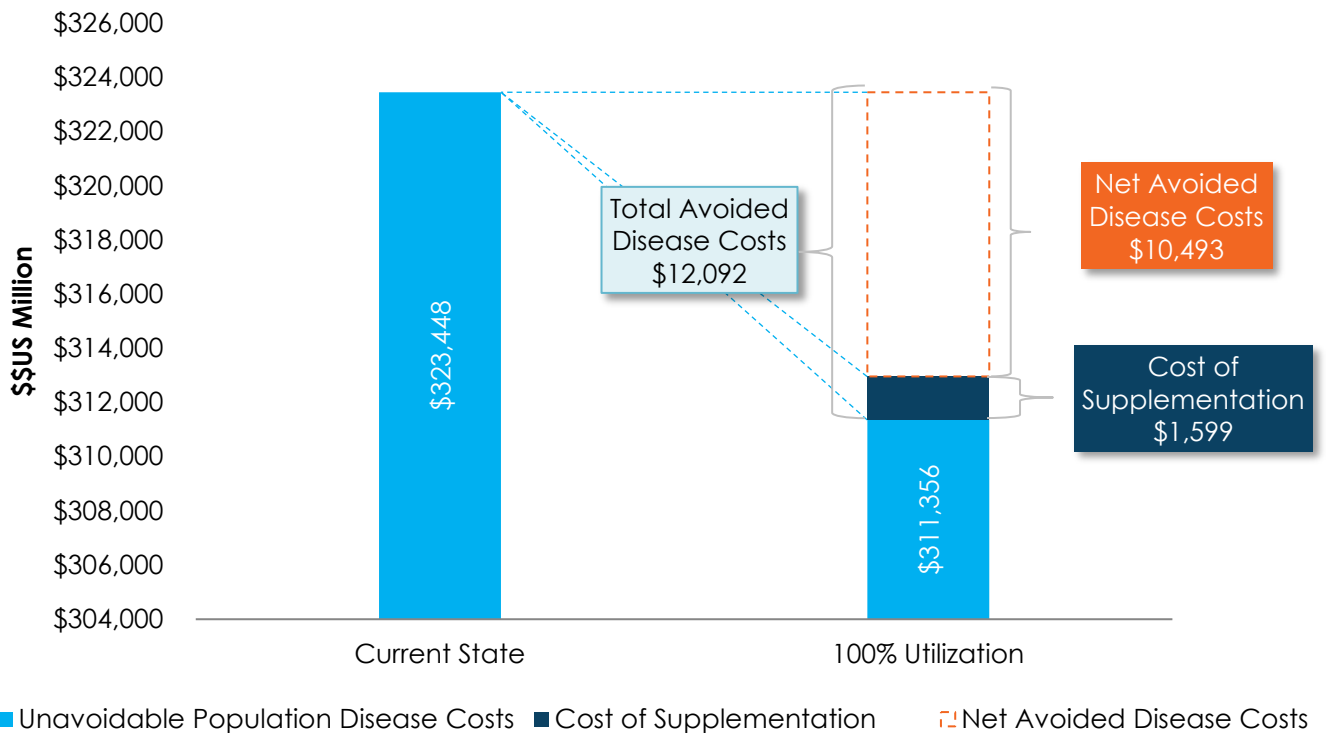
Based the incurred cost of vitamins B6, B9 and B12 dietary supplementation, the net cost savings expected from reduced health care-attributed expenditures in 2022 derived from avoided dementia transition events would have been \$10.49 billion in 2022 or \$109.93 billion in cumulative net savings during 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



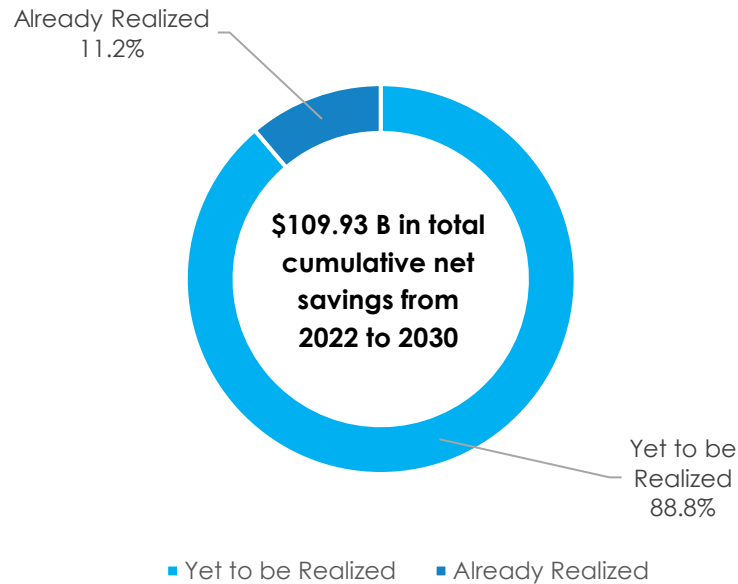
Note: B indicates billion. Source: Frost & Sullivan analysis

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 to 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.



Council for Responsible Nutrition

The Science Behind the Supplements