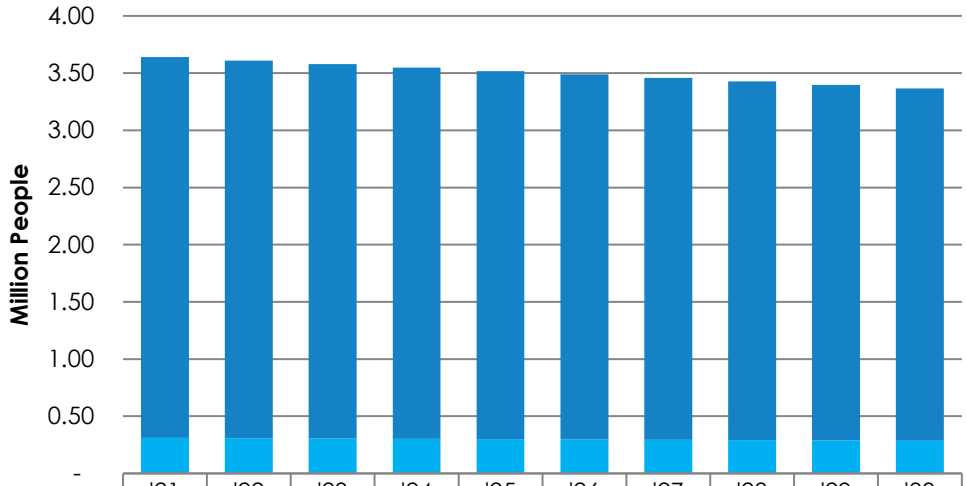
REDUCTION IN EARLY CHILDHOOD COGNITIVE DEVELOPMENT DISORDERS DUE TO INADEQUATE MATERNAL CHOLINE INTAKE DURING PREGNANCY FROM CHOLINE SUPPLEMENT USE

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

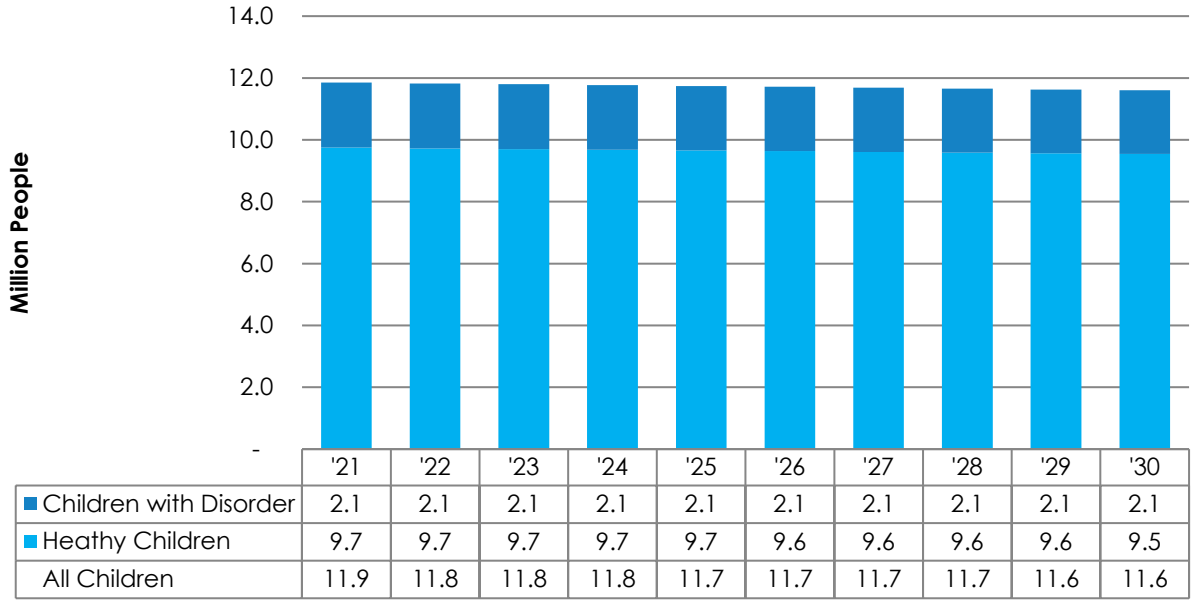
Source: Wallace et al. 2017m, Korsmo et al. 2019, Derbyshire et al. 2020. Centers for Disease Control and Prevention, US Census, and Frost & Sullivan analysis

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

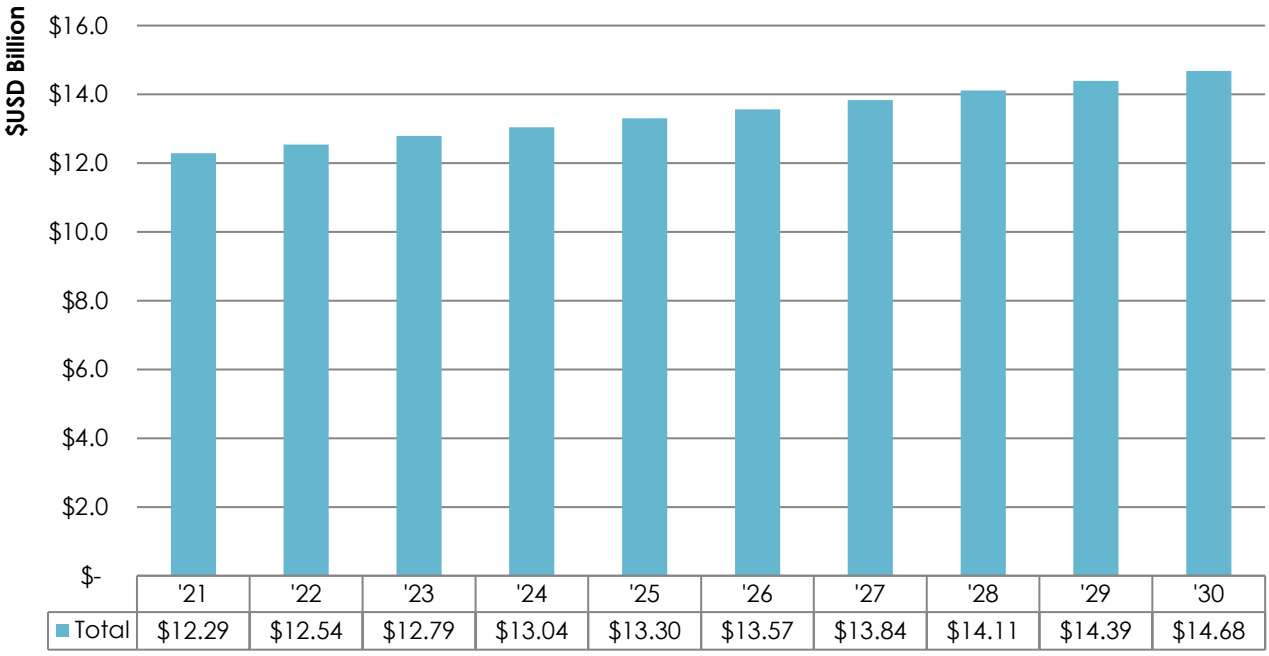
Year	Inadequate Maternal Choline Intake & Childhood Cognitive Development, Cost per Person Case, $ per Child	Inadequate Maternal Choline Intake & Childhood Cognitive Development, Total Cost ($ billion)
2021	$5,844	$12.293
2022	$5,974	$12.538
2023	$6,108	$12.787
2024	$6,244	$13.042
2025	$6,384	$13.302
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



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.

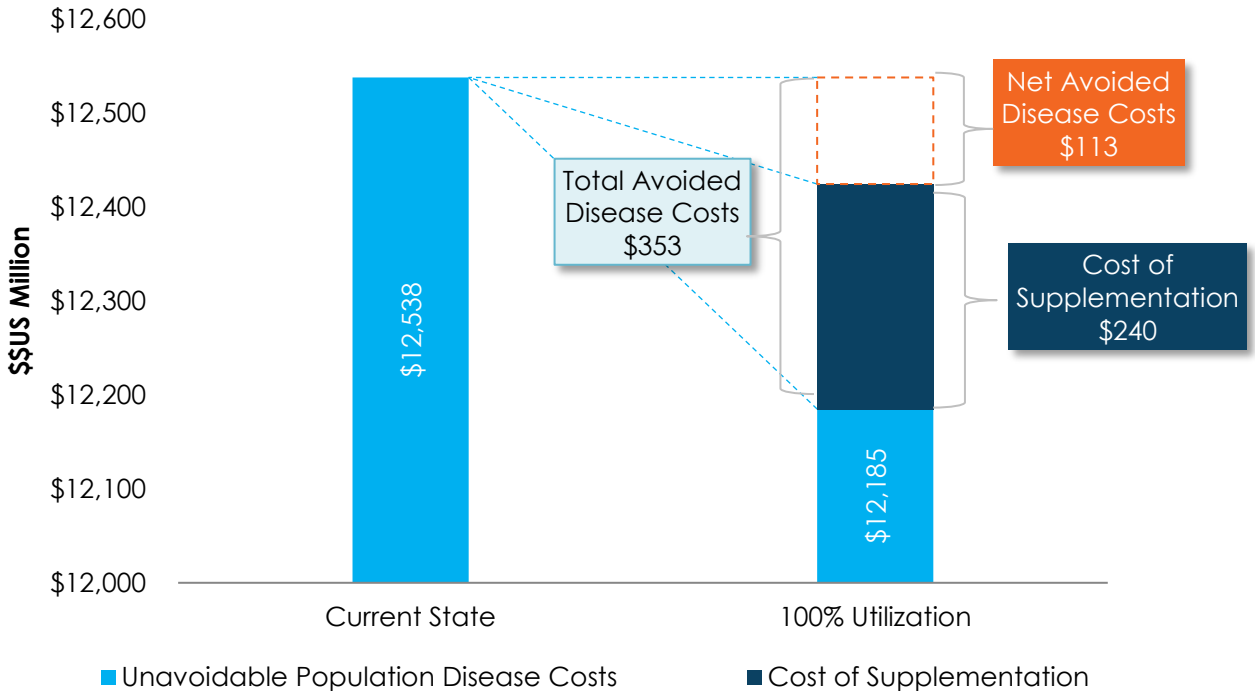
Table 87. Choline Cost Analysis: Summary Results—Cost of Dietary Supplementation of the Target Population*, 2022-2030

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

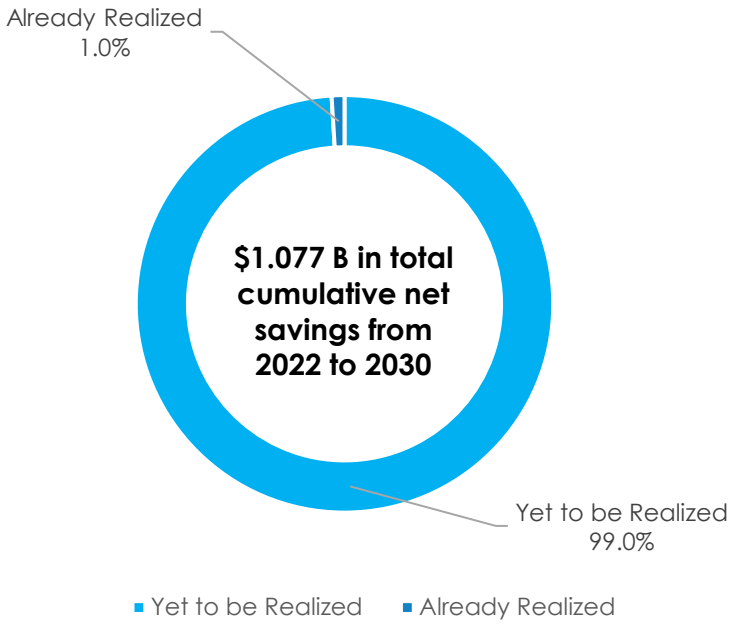
Metric	Measure
Avoided Early Childhood Cognitive Development Disorders-attributed care expenditures given mother Choline supplement intervention per year, 2022	$353 M
Average avoided Early Childhood Cognitive Development Disorders-attributed hospital utilization expenditures given Choline supplement 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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