



# **The Real Deal on Brain Health Supplements:** GCBH Recommendations on Vitamins, Minerals, and Other Dietary Supplements

Global Council on  
**Brain Health**<sup>SM</sup>  
A COLLABORATIVE FROM AARP

# Background: About GCBH and its Work

The Global Council on Brain Health (GCBH) is an independent collaborative of scientists, health professionals, scholars and policy experts from around the world who are working in areas of brain health related to human cognition. The GCBH focuses on brain health relating to people's ability to think and reason as they age, including aspects of memory, perception and judgment. The GCBH is convened by AARP with support from Age UK to offer the best possible advice about what older adults can do to maintain and improve their brain health. GCBH members gather to discuss specific lifestyle habits that may impact people's brain health as they age, with the goal of providing evidence-based recommendations for people to consider incorporating into their lives.

Many people across the globe are interested in learning that it is possible to influence their own brain health and in finding out what can be done to maintain their brain health as they age. We aim to be a trustworthy source of information, basing recommendations on current evidence supplemented by a consensus of experts from a broad array of disciplines and perspectives.

## Supplements and Brain Health

Members of the GCBH met in Washington, D.C., to address the topic of dietary supplements and brain health for people age 50 and older. Throughout the discussion, experts examined the evidence on whether the consumption of dietary supplements can impact people's cognitive function as they age. Participants are listed in Appendix 1.

This paper summarizes the consensus reached by the experts and describes the major points of discussion that led to their recommendations. It also identifies gaps in our knowledge

about dietary supplements and brain health, provides a glossary of terms used in the document and lists resources for additional information. This paper is not intended to be a systematic, exhaustive review of all pertinent scientific literature on the topic. Rather, the selected references provided at the end of the document give helpful background material and present a sizable sample of the current evidence underpinning the GCBH consensus in this area.

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# Introduction

Dietary supplements or, more commonly, “supplements,” are products taken by mouth that contain a “dietary ingredient.” Dietary ingredients include vitamins, minerals, amino acids, botanicals (including herbs) and enzymes, as well as other substances alone or in combination that can be used to supplement one’s diet. Supplements come in many formulations, including pills, capsules, tablets, powders, food bars and liquids.

In 2018 an estimated 85,000 types of dietary-supplement products were sold in the United States alone, according to the Nutrition Business Journal, with more than \$40 billion in retail sales in the United States and \$121 billion worldwide. In conjunction with this report, AARP surveyed a representative sample of adults 18 and older on their use of dietary supplements.<sup>1</sup> Among adults age 50 and older, 81 percent believe that supplements are at least somewhat important for overall health. Sixty-nine percent are currently taking a dietary supplement at least three times a week.

The United States Government Accountability Office (GAO) recently examined available data and found that memory supplements were a small but growing portion of the overall market for dietary supplements. In the United States their sales nearly doubled in value from 2006 to 2015, increasing to \$643 million in 2015. According to an industry forecast report, the brain-health supplements generated \$3 billion in sales globally in 2016, and that figure is projected to reach \$5.8 billion by 2023. Given the vast interest people have in maintaining and improving their brain health as they age, the GCBH has no doubt that the use of brain-health supplements targeted at an increasingly aging population worldwide is growing and large numbers of people are already taking them. The 2019 AARP Brain Health and Dietary Supplements Survey shows that more than a quarter of Americans age 50 and older are regularly taking supplements for their brain health. Twenty-six percent of adults take at least one supplement for brain-health reasons. Among adults specifically taking dietary supplements for brain health, 21 percent report taking dietary supplements to maintain — and 20 percent report taking them to improve — their brain

health. Interestingly, 11 percent report currently taking a supplement to delay the onset of dementia, and 8 percent say they take a supplement in order to reverse dementia.

In this document we summarize the state of the scientific evidence on whether dietary supplements currently on the market can benefit the brain health of adults, focusing primarily on those age 50 and older. We discuss a broad range of issues pertaining to supplements and cognitive health. We examined the evidence relating to vitamin and mineral supplements, focusing primarily on the eight B vitamins, and vitamins D and E. We also discussed other well-known supplement ingredients commonly marketed for brain health including: the omega-3 fatty acids docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and alpha-linolenic acid (ALA); fish oil; medium-chain triglycerides (coconut oil); huperzine-A; caffeine; nicotinamide riboside; phosphatidylserine; curcumin; flavanols; coenzyme Q10 (CoQ10); ginkgo biloba; and apoaequorin (derived from jellyfish).

These consensus statements and recommendations are based on the GCBH experts’ knowledge of the field and their evaluation of the best available evidence from peer-reviewed, published observational studies and randomized controlled trials in humans, as well as studies conducted in animals designed to help determine the effects of dietary supplements on brain health.

The context in which dietary supplements are manufactured and sold also played an important role in the consensus and the resulting recommendations. Around the world, manufacturers are generally prohibited from selling unsafe ingredients, but we are aware of no country that regulates or evaluates dietary supplements for effectiveness before they are permitted to be sold. There is also no global consensus on how these types of products should be defined or regulated. For example, regulators consider melatonin to be a dietary supplement in the United States, a natural health product in Canada, but a prescription medicine in Australia. Regulations and government oversight of dietary

1. 2019 AARP Brain Health and Dietary Supplements Survey, fielded Jan. 30, 2019, to Feb. 7, 2019, from a nationally representative sample that included 1,747 adults age 18 and older (809 adults age 50 and older). Oversampling augmented the number of African American/Black, Hispanic/Latino and Asian adults to achieve a total sample for each group of 350, 350, and 200 adults age 18 and older, respectively. The margin of error is +/- 2.4 percentage points.

supplements differ significantly from country to country. (See more on international regulation of the supplement industry in the “Discussion” section.) Quality can vary from product to product, and concerns have been raised about the content, identity, purity, potency and potential toxicity of certain supplements. The lack of accepted testing methods and standards impacts the ability of regulators worldwide to identify and analyze the ingredients. The GCBH believes that more high quality clinical studies of the safety and efficacy of dietary supplements on brain health outcomes in humans are needed. It is essential that such studies include quality assurance to ensure the supplements being used contain the ingredients and amounts the manufacturers claim, and nothing else.

A significant lack of understanding exists about how the level of regulatory scrutiny for dietary supplements differs from prescription drugs and over-the-counter medications. For example, in the United States, a prescription drug has to demonstrate safety and efficacy to the Food and Drug Administration (FDA) prior to market approval. Before a prescription drug or over-the-counter drug can be sold, it has to demonstrate clear evidence of a positive effect, it must be thoroughly tested for safety and all side effects found must be reported to the FDA. However, the same level of government

review and approval are not required for dietary supplements before they are put on the market.

People often think that supplements are subject to the same government regulations as prescription and over-the-counter drugs. AARP’s 2019 survey reveals that almost half of older adults (49 percent) in the United States mistakenly believe the FDA determines that dietary supplements, including vitamins, are both safe and effective before they are sold, while 36 percent believe that herbs and enzymes receive the same scrutiny. In fact, the FDA’s mandatory premarket evaluation of the safety, effectiveness, and health and medical claims of drugs does not apply to dietary supplements. It is against the law for supplement manufacturers to make claims that they treat diseases such as Alzheimer’s. Both the FDA and the Federal Trade Commission (FTC) require that such claims be substantiated by competent and reliable scientific evidence before they are made. However, the substantiation requirement is not generally reviewed by the regulatory agencies. These agencies can only take enforcement action against unsubstantiated or false claims once the product is already on the market. This situation may lead many people to have a false sense of security when it comes to taking dietary supplements they find on store shelves or online.

# CONSENSUS STATEMENTS

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These consensus statements and the recommendations that follow are based on extensive sources and research within nutrition, neurology, psychology, psychiatry, epidemiology, neuroendocrinology, basic science, randomized controlled trials and observational studies. The results of such studies were published in peer-reviewed journals. Definitions of the terms used in the consensus, recommendations and practical tips are provided in the “Discussion” section and the glossary in Appendix 2. Greater detail about commonly available types of dietary supplements sold for reasons related to brain health are provided in the “Discussion” section.

1. For most people, the best way to get your nutrients for brain health is from a healthy diet.
2. We do not endorse any ingredient, product or supplement formulation specifically for brain health, unless your health care provider has identified that you have a specific nutrient deficiency.
3. Consumers should not begin taking any supplements for brain health without first consulting with their health care provider.
4. Vitamins and minerals that are essential for health in small doses may be harmful if taken in excess. More is not necessarily better.
5. In general, there is insufficient evidence that multivitamins will improve brain health. Multivitamins are not a substitute for a healthy diet in promoting and maintaining brain health.
6. Very few supplements have been carefully studied for their effect on brain health. For the handful that have been researched, several well-designed studies of supplements for brain health found no benefit in people with normal nutrient levels. It's unclear whether people with nutritional deficiencies can benefit their brains by taking a supplement, because the research is inconclusive.
7. Aging is linked with health conditions such as failure to absorb nutrients and poor dental health that may increase risk of vitamin deficiencies that could result in poor brain health. Use of multiple medications can also increase risk of vitamin deficiencies.
8. Problems with cognitive function, including thinking skills and memory, have been associated with deficiencies in certain nutrients (e.g., vitamin B12); however, there is no convincing evidence to recommend daily dietary supplements for brain health in healthy older adults.
9. Vitamin B12 deficiency and folate deficiency (also known as vitamin B9 deficiency) may negatively affect your brain health; therefore, supplementation may be beneficial for people with lower-than-recommended levels of these B vitamins.
10. Consumption of fatty fish, as well as other types of seafood, may benefit cognitive function. This may be due to their omega-3 fatty acid content, in particular DHA, but this is not proven. Overall, there is insufficient evidence to recommend taking a fish oil-derived omega-3 supplement for brain health.
11. Vitamin D deficiency can be an issue for older adults, and your health care provider may recommend vitamin D supplementation to correct low levels for general health. However, there is insufficient evidence that vitamin D supplementation benefits brain health.
12. Beyond the nutrients mentioned above that are taken to replace an identified deficiency, there is insufficient evidence that other supplements benefit brain health.
13. Supplement manufacturers and distributors often make vague or exaggerated claims about brain health. Because dietary supplements are marketed without premarket governmental review of their safety and efficacy or the truthfulness of their claims, consumers should approach claims made on supplement packaging and in marketing materials with skepticism.
14. The quality of the ingredients in supplements can vary widely. The ingredients in supplements are not generally reviewed for purity and content by government agencies before they are allowed to be sold. Some may contain ingredients that could harm consumers.
15. The GCBH encourages manufacturers of dietary supplements to conduct, support and publish rigorous human studies that are independently reviewed by other scientists who can evaluate supplements' effects on brain health.

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2. Randomized controlled trials and epidemiological observational studies are defined in the Glossary in appendix 2. An overview of the differences, strengths and limitations of the two study types in humans is listed in appendix 4.

# EXPERT RECOMMENDATIONS

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## FOR INDIVIDUALS:

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1. Rather than turning to supplements to boost brain health, choose foods known to support a healthy brain. See *Brain Food: [GCBH Recommendations on Nourishing Your Brain Health](#)* for recommendations.
2. Consult your health care provider if you are considering taking a supplement, and ask about the risks, benefits and medication interactions. We do not recommend taking dietary supplements for brain health unless your health care provider has determined you are nutrient-deficient or are at risk of becoming so (i.e., for reasons of deficiencies caused by diet, lifestyle, certain surgeries or other health issues).
3. Carefully check ingredients and information on supplement labels. Be aware that product labels may not reflect the actual ingredients or their amounts in the supplements. Products often contain less or more of what they claim. In some cases, there may be additional ingredients not listed on the label at all, some of which may be harmful to your health.
4. Verify the quality of evidence about the product's effectiveness, purity and quality. (For further information on how to do this, see "Practical Tips.")
5. If you are experiencing significant memory loss, consult your health care provider, who may wish to check your folate and B12 levels. Individuals should follow their health care provider's advice to make sure the supplements taken are appropriate to address their specific deficiency or problem. Make sure you do not take too much of any of the B vitamins and check to see if the foods you eat are already fortified with them. If your health care provider advises that you take folic acid, ask whether you should take it with vitamin B12. Vitamin B "complex" supplements contain different mixtures of B-vitamins at different doses, not all of which are needed by a particular individual.
6. Although caffeine may provide some short-term benefits in mental alertness and focus, caffeine supplements in the form of energy drinks and pills may carry health risks and are not recommended.

## FOR HEALTH CARE PROVIDERS:

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1. Routinely ask about your patients' use of any dietary supplements. This is important in order to identify and manage older adults who are potentially at risk of adverse drug interactions and unnecessary expenditures. Large percentages of older adults routinely take several supplements and may not volunteer that information when asked about medications.
2. Recommend healthy lifestyle and dietary interventions shown to be effective at promoting brain health.
3. Evaluate your patients for potential vitamin and mineral deficiencies. In people with normal test results and levels of nutrition, there is not sufficient evidence to recommend general supplementation.

## FOR THOSE WITH MILD COGNITIVE IMPAIRMENT (MCI), DEMENTIA, OR OTHER BRAIN DISORDERS:

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1. Adopt healthy lifestyle habits. Work with your health care provider to ensure that you do not have any vitamin or mineral deficiencies that need correcting. See additional [GCBH reports](#) for details on a brain-healthy lifestyle.
2. Scientific evidence does not support the use of any supplement to prevent, slow, reverse, or stop MCI or dementia or other related neurological disease.
3. Melatonin is not recommended for older people with dementia due to risk of increased falls and other adverse events, according to 2015 guidelines from the American Academy of Sleep Medicine. See the GCBH report "[The Brain-Sleep Connection](#)" for more on melatonin's use as a sleep aid.
4. There is insufficient evidence to support the use of popular (and often expensive) medical foods or dietary supplements being marketed to older adults for brain health. For example, Souvenaid is a medical food sold in Europe and Asia for the purpose of improving symptoms in those with mild or early Alzheimer's disease. In Hong Kong, it is available over-the-counter without a prescription. It is not approved for sale in the United States. Until there is evidence of effectiveness, these products are not recommended for brain health.

# PRACTICAL TIPS

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- 1. Save your money.** Buying supplements to benefit your brain health is likely a waste of your money.
- 2. If it sounds too good to be true, it probably is.** Beware if a supplement claims to improve brain health or memory, make you smarter, or cure a brain disease.
- 3. Show your health care provider what you are taking.** The next time you see your health care provider, take all your vitamins and other supplements to your appointment so you can discuss them.
- 4. Think before you buy.** If you are thinking of taking a vitamin or other supplement, ask yourself these questions:
  - a. Am I getting enough of this nutrient in my diet?
  - b. Am I eating foods—such as some cereals or orange juices—that are already fortified with it? Remember that energy drinks, bars and powders often have added vitamins and minerals.
  - c. Am I taking a multivitamin that already provides the recommended intake of nutrients that I need?
  - d. What improvements do I expect this supplement to make?
  - e. Are claims about the supplement’s benefits supported by high-quality research? To figure that out, in addition to reading this report, look at reputable websites such as the National Institutes of Health Office of Dietary Supplements, the National Center for Complementary and Integrative Health, and Cognitive Vitality, a program of the Alzheimer’s Drug Discovery Foundation.
  - f. Does the supplement have any side effects or interfere with medications I’m taking? Just because a supplement is “natural” doesn’t mean it’s necessarily good for you or safe. Supplements can strengthen or weaken the effects of medications.
  - g. How long do I need to take it?
- 5. Read labels carefully.** Know what supplement or supplements you are buying, and don’t buy supplements with ingredients you don’t want or need.
- 6. More is not always better.** Make sure you don’t take more than you should. What might be OK in small amounts might not be in larger ones. Read the supplement label for the serving size. Some vitamins, minerals, and other ingredients in supplements can be toxic at high levels. For example, large doses of vitamins A, D, E and K, as well as excess iron and caffeine, can cause problems.
- 7. Check the expiration date.** Supplements lose potency over time.
- 8. Look for third-party verification of quality.** Because of inconsistencies in product quality, look for products that have been tested by an independent third party such as:
  - a. ConsumerLab.com, [www.consumerlab.com](http://www.consumerlab.com)
  - b. NSF International, [www.nsf.org](http://www.nsf.org)
  - c. U.S. Pharmacopeia (USP), [www.usp.org](http://www.usp.org)
- 9. Check for cautions and warnings related to your specific health conditions.** People with certain health conditions should be especially careful about taking dietary supplements. These include:
  - a. *People on certain medications.* Such medications include blood thinners, heart medications, steroids and drugs that affect the immune system. Sudden increases in your vitamin K intake, for example, decrease the effect of the blood thinner Coumadin.
  - b. *People who are about to have surgery.* Herbal medications such as echinacea, garlic, ginkgo, ginseng, kava, saw palmetto, St. John’s wort and valerian can increase risks during surgery, according to the American College of Surgeons. Make sure you tell your surgeon about any vitamins, minerals or other supplements you are taking.
  - c. *People who have cancer.* Some vitamins and supplements may make your condition worse. Antioxidant vitamins such as vitamins E and C, for example, may reduce the effectiveness of chemotherapy.

# DISCUSSION

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## **Process used to produce the consensus and recommendations**

Issue specialists from around the world who are leaders in their fields were selected to participate on the GCBH panel on brain health and supplements. These experts have conducted research that has significantly contributed to the body of evidence examining the impact of dietary supplements, and many have studied the impact on brain health in older adults. Their diverse areas of expertise represent perspectives from disciplines including nutrition, epidemiology, genetics, geriatric psychiatry, gerontology, internal medicine, neurology, neuroscience, public health, and dietary supplement testing and regulation.

Fourteen issue specialists from four continents were asked to critically examine the state of the science in October 2018. They discussed findings from epidemiological studies as well as randomized controlled trials. The experts considered the cumulative body of evidence to determine whether it is sufficient to issue recommendations for supplement use by individuals to maintain and/or improve brain health. As a framework to guide their deliberations, the issue specialists considered numerous questions, which are listed in Appendix 3.

After an in-depth moderated discussion, several follow-up conference calls and an exchange and refinement of drafts over several months, the issue specialists arrived at 15 consensus statements. These summarized the weight of the available evidence on the impact of dietary supplements on brain health. Based on their consensus that supplements have not been proven to be effective at improving brain health unless it is to correct a specific, identified nutrient deficiency, they made numerous recommendations to individuals and health care providers related to supplements in the context of brain health and cognitive decline. Further, they agreed on practical tips to help people decide whether to take dietary supplements for their brain health and show them what to watch out for if they do take them.

Liaisons from government and nonprofit organizations with relevant expertise in brain health, supplements and regulation were invited to provide input and technical feedback during the refinement of the draft recommendations.

Seven members of the council's governance committee participated in the meeting in Washington, D.C. The entire governance committee reviewed and finalized the document during subsequent conference calls and emails. The governance committee members issuing the recommendations are independent health professionals representing diverse expertise across three continents in epidemiology, psychology, public health, neurology, psychiatry, geriatrics, cognitive neuroscience, neuropsychology, pharmacology, medical ethics, health policy and neurodegeneration. The governance committee applied their expertise to determine whether they concurred with the statements and to evaluate the objectivity and feasibility of the proposed recommendations and practical tips. The committee also reviewed the document to decide whether it accurately reflected the expert opinions expressed and the current state of science in the field. The GCBH governance committee approved the document on May 17, 2019.

## **Guiding principles underlying the expert consensus and recommendations**

Science and knowledge of brain health are continually evolving. These recommendations are based upon the current state of scientific and medical knowledge in order to provide people with reliable information on what is known and not yet understood about the relationship between dietary supplements and brain health. Waiting until definitive evidence exists on all the issues related to supplements and cognitive health would mean that we would not be able to provide practical guidelines to people who are seeking answers now. The GCBH feels confident in making these recommendations for people to incorporate into a healthy lifestyle in order to help maintain and improve their brain health.

In general, these recommendations are meant for all healthy adults, with a particular focus on men and women age 50 and older who have not been diagnosed with a neurodegenerative disease such as Alzheimer's (except where otherwise specified). The intent is to be as inclusive as possible for people as they age. The information in the following sections on vitamins and other supplements is based on expert discussions and input as well as material from peer-reviewed scientific journals, the National Institutes of Health's [Office of Dietary Supplements](#), the [Alzheimer's Drug Discovery Foundation](#), [Cognitive Vitality](#) and [ConsumerLab.com](#).

## Introduction to vitamins, minerals, and other dietary supplements

Vitamins and minerals are essential for your body to function properly. There are 13 vitamins—vitamins A, C, D, E, K, and the eight B vitamins. The essential minerals include calcium, phosphorus, potassium, sodium, chloride, magnesium, iron, zinc, iodine, sulfur, cobalt, copper, fluoride, manganese, and selenium. Vitamins and minerals have many different roles in the body. They help you resist infections, keep your nerves healthy, help your body get energy from food and help your blood to clot properly. By following a healthy, varied diet most people will get enough of most of these vitamins and minerals from food. See the GCBH report “[The Brain-Food Connection](#)” for more information about eating a healthy diet for your brain, and see the [USDA Dietary Guidelines](#) for recommendations for an overall healthy diet. If there is a recommended daily amount from the United States government, we’ve included it below.

In general, dietary supplements are not necessary for brain health or overall health. In this report, we address specific ingredients (vitamins, minerals, and others) in dietary supplements that people take for brain health. It is important to note that any benefit from taking supplements is dwarfed by the benefits of a brain-healthy lifestyle. For specific details of how to integrate the best habits around sleep, diet, stress, exercise, social connections and brain-challenging activities into your life, see separate Global Council on Brain Health reports at [globalcouncilonbrainhealth.org](http://globalcouncilonbrainhealth.org).

### Vitamins

**Multivitamins.** Multivitamins, often in combination with minerals, are the most commonly purchased class of dietary supplement products, with close to half of adults taking them. Talk to your health care provider about whether you should take a multivitamin, as most people don’t need them. Only those who do not have a balanced diet and those with certain health conditions may benefit from a multivitamin. Read the label to make sure doses aren’t too large and avoid taking supplements with mega doses as certain vitamins and minerals can be harmful at high levels. Also pay attention to how many vitamins and minerals you are getting from fortified foods such as cereal, milk, orange juice and bread. The 2019 AARP survey found that 42 percent of adults age 50 and older take a multivitamin.

Below we provide some additional information on select vitamins and nutrients.

**B vitamins.** The B vitamins include B1 (thiamin), B2 (riboflavin), B3 (niacin), B5 (pantothenic acid), B6 (pyridoxine), B7 (biotin), B9 (folate) and B12 (cobalamin).

These vitamins help the body make energy from the foods you eat. The body needs all the B vitamins. Although there are many types of B vitamins, B6, folate (B9) and B12 have been the most widely studied in relation to brain health. There have been inconsistent findings on the effect of the combinations of using B12, folate (B9) and B6 in order to protect or improve brain health, which we discuss in greater detail below. Among Americans 50 and older, 26 percent take a B vitamin, and among those taking a B vitamin, 4 percent are taking B9, 48 percent are taking B12 and 62 percent are taking a B complex. (2019 AARP survey).

**Vitamin B12.** Vitamin B12 helps keep brain cells, nerve cells and blood cells healthy. Vitamin B12 is found in beef liver, clams, red meat, pork, fish, milk, other dairy products and some fortified breakfast cereals. Most people get enough B12 from the foods they eat. Older adults can have trouble absorbing B12—especially if they are on acid-reducing medicines—and may need to get the vitamin through fortified foods or a supplement. In the United States, between 4.4 percent to 15 percent are estimated to have a B12 deficiency, and close to 20 percent of those over age 60 in the United Kingdom are estimated to be deficient in B12. Some people have a disease called pernicious anemia that causes them to have trouble absorbing B12 even from dietary supplements. Vegans and vegetarians can have trouble getting enough B12 from foods because only animal foods have B12 naturally. Evidence has shown that Vitamin B12 deficiency may be linked to a number of health problems including weakness, tiredness, numbness/tingling in the hands and feet, depression, confusion, poor memory and, if untreated, even dementia. If you have any of these symptoms and suspect you may have a B12 deficiency, ask your doctor to be tested. For those who do not have a documented deficiency, there is not enough evidence to recommend taking B12 supplements to prevent cognitive decline or dementia.

LIFE STAGE	RECOMMENDED AMOUNT
Adults	2.4 mcg

*Source: Food and Nutrition Board of the National Academy of Sciences, Engineering, and Medicine*

**Folate (B9).** Folate is a B vitamin that the body needs for brain health, nerve function and the production of red blood cells and DNA. Folic acid is the synthetic form of folate that is added to fortified foods and is included in most dietary supplements. Folate is found in many vegetables, especially asparagus, brussels sprouts and dark green leafy green vegetables like spinach and collard greens. Because a folic acid deficit at pregnancy can lead to birth defects,

all enriched grain products—such as breads, cereals and enriched flour—are required to include folic acid in the United States. Because of this, folate deficiency is rare in the United States but is more common in other countries. Folic acid supplements, with or without other B vitamins, have not yet been found to improve cognitive function or prevent dementia or Alzheimer’s disease, but more research is needed. Taking high doses of folic acid may cause some health problems, including possibly speeding up the development of some cancers and aggravating complications from B12 deficiency as well as negative interaction with some drugs.

LIFE STAGE	RECOMMENDED AMOUNT
Adults 19+ years	400 mcg DFE
Pregnant teens and women	600 mcg DFE
Breastfeeding teens and women	500 mcg DFE

Source: Food and Nutrition Board of the National Academy of Sciences, Engineering, and Medicine

**Vitamin B6.** Vitamin B6 is involved in more than 100 different reactions involved in metabolism as well as immune functioning. Vitamin B6 is found in poultry, fish, organ meats, potatoes and fruits other than citrus. Most people get enough vitamin B6 from their diets and deficiency is uncommon in the United States. People with rheumatoid arthritis, Crohn’s disease, inflammatory bowel disease and several other autoimmune disorders sometimes have low vitamin B6 levels. Symptoms of low vitamin B6 levels include numbness and tingling in the hands and feet, depression, confusion and a weakened immune system. Long-term B6 supplementation can sometimes cause limb pain and balance difficulties. Thus, it is important to know whether your diet and supplements together may put you at risk for B6 toxicity.

LIFE STAGE	RECOMMENDED AMOUNT
Adults 19-50 years	1.3 mg
Adults 51+ years (men)	1.7 mg
Adults 51+ years (women)	1.5 mg

Source: Food and Nutrition Board of the National Academy of Sciences, Engineering, and Medicine

**B vitamins as a means of lowering homocysteine levels.** Homocysteine is a common amino acid in the blood. High levels are linked to increased risk of stroke and cognitive decline, but the exact cause is not clear. Folic acid taken by itself or with vitamin B12 or vitamin B6 can lower homocysteine levels, but studies in humans testing whether folic acid, vitamin B12 and vitamin B6 supplements can lower stroke and dementia risks have had mixed results.

More research is needed to identify subgroups of people who may benefit from B vitamins.

**Vitamin D.** Vitamin D comes from food sources or when sunlight stimulates the body to make it. It is important for calcium absorption and nervous system function, and helps the immune system fight off bacteria and viruses. Fatty fish such as salmon, tuna and mackerel are among the best food sources, and liver, cheese and egg yolks contain it in smaller amounts. Some foods such as milk and cereal often have added vitamin D. The body makes vitamin D when the skin is exposed to sunlight, although sun exposure increases the risk of skin cancer. One common recommendation is that older people get 15 minutes of sunshine on unexposed arms and legs three times a week. Note that sunscreen does block vitamin D absorption. Older people, those with dark skin, people who are obese and those who don’t get direct sun exposure are at risk for vitamin D deficiency. Vitamin D supplementation is sometimes recommended for reducing the rate of bone loss in the elderly or strengthening bone health. For example, post-menopausal women are frequently advised to take vitamin D and calcium for prevention of osteoporosis. The 2019 AARP survey found that 46 percent of Americans 50 and older are taking vitamin D, and 43 percent are taking it for bone health.

Although some (but not all) studies have linked low levels of vitamin D to memory problems and dementia, and a few small studies suggest that taking vitamin D may improve some brain function, overall, there is not enough evidence to say that taking vitamin D pills can protect against dementia or to recommend taking it to improve or protect memory.

For more information, see the National Institutes of Health Office of Dietary Supplements’ [fact sheet on vitamin D](#) and Cognitive Vitality’s [vitamin D rating](#).

LIFE STAGE	RECOMMENDED AMOUNT
Adults 19-70 years	600 IU
Adults 71 years and older	800 IU

Source: Food and Nutrition Board of the National Academy of Sciences, Engineering, and Medicine

**Vitamin E.** Vitamin E is also essential to meeting your body’s needs. Yet while it helps the immune system function properly, too much can be toxic. Vitamin E is found in vegetable oils such as sunflower and safflower oils, nuts such as walnuts and almonds, sunflower seeds, and green vegetables such as spinach and broccoli. Many breakfast cereals and some other foods are also fortified with vitamin E. Some (but not all) studies have reported that people who consume high levels of vitamin E through food may have a

lower risk of dementia, but vitamin E supplements do not seem to offer protection for the brain.

One clinical trial studying people with mild to moderate Alzheimer’s disease found that those who took 2000 IU/day (far above the recommended daily amount) of vitamin E had a slower decline in their ability to do activities of daily living than those in the study who were not taking vitamin E. However, the same study found no effect on cognitive abilities such as memory and reasoning. It is unclear whether the possible benefits of vitamin E supplementation for people living with Alzheimer’s would apply to people who already have adequate levels of the vitamin. Vitamin E deficiency can cause health problems such as muscle weakness and vision problems. However, deficiency is rare except in those who have certain diseases where fat is not properly absorbed, such as Crohn’s disease.

High doses of vitamin E taken as a supplement increase the risk of serious bleeding in the brain. Vitamin E can increase the risk of dangerous bleeding in those taking some medicines such as warfarin (Coumadin). One study found that men who took vitamin E every day for several years had an increased risk of prostate cancer. A few studies have found that vitamin E may increase risk of death, especially in high doses or in those who are in poor health. Because of these risks, the upper recommended limit for adults in the United States is 1,500 IU/day for supplements made from the natural form of vitamin E and 1,100 IU/day for supplements made from synthetic vitamin E.

Although there is some evidence that vitamin E may slow decline in performance of activities of daily living in patients with Alzheimer’s dementia, there is insufficient evidence that vitamin E supplementation will maintain people’s ability to think and reason as they age.

LIFE STAGE	RECOMMENDED AMOUNT
Adults	15 mg (22.4 IU)

Source: Food and Nutrition Board of the National Academy of Sciences, Engineering, and Medicine

### Other dietary supplements marketed for brain health

**Apoaequorin (jellyfish).** Apoaequorin is a protein isolated from the *Aequorea victoria* jellyfish. It is the active ingredient in Prevagen, a dietary supplement marketed for memory and brain health. One clinical trial, funded by the supplement manufacturer, reported that apoaequorin improved cognitive function in older adults, but that study did not compare the group taking the apoaequorin supplement with a control group, so the study didn’t show

that apoaequorin works better than a placebo. A second clinical trial, also funded by the company, failed to show a statistically significant improvement in the experimental group over a placebo group as a whole. The chemical structure of apoaequorin is likely broken down in the gut before reaching the brain, so it’s unlikely for it to have any brain benefits. The panel does not recommend taking apoaequorin for brain health.

Note: AARP has joined other advocacy organizations arguing that the manufacturers’ claims that Prevagen can treat age-related memory loss have no basis in science. At the time of publication of this report, a United States Court of Appeals is allowing the Federal Trade Commission and the state of New York to proceed to court to prove that Prevagen’s claims that it “improves memory and provides other cognitive benefits” are deceptive.

**Caffeine.** Caffeine is a stimulant found in coffee, tea and energy drinks as well as kola nuts and guarana. It is an ingredient in many supplements. It is used to improve endurance and power in sports and is found in a number of supplements that are marketed to improve memory and concentration. Although caffeine has shown short-term effects on memory, focus and concentration, there is not enough evidence to recommend its use for a long-term cognitive supplement for brain health. Caffeine in high doses, such as those found in some energy drinks, can have adverse effects including insomnia, nervousness, headache and even seizures. Emergency room visits involving energy drinks increased tenfold between 2005 and 2011, to more than 20,000, according to the Substance Abuse and Mental Health Services Administration. Most of those emergency room visits were by 18- to 25-year-old males, although visits in those over age 40 was growing rapidly, according to the report.

**Coenzyme Q10 (CoQ10).** CoQ10, also known as ubiquinone, is used by the body to convert food into energy. It is found in foods such as vegetable oils, fatty fish, organ meats, whole grains and some fruits. Studies in humans have not convincingly shown benefits for thinking, memory or Alzheimer’s protection. It may increase the risk of blood clotting in those taking medications for high blood pressure. There is not enough evidence to recommend taking CoQ10 for protecting the aging brain or preventing or treating Alzheimer’s disease.

**Curcumin and turmeric.** Turmeric, a plant related to ginger, is used as a common spice and a major ingredient in curry powder and a common traditional medicine in India and

Asia. Its prime active ingredients are curcuminoids—including curcumin—which give turmeric powder its yellow orange color. Turmeric and curcumin have been studied for a variety of health conditions including heart attacks, knee pain, skin irritation, cancer, diabetes and Alzheimer’s disease.

A recent double-blind placebo-controlled study of a bioavailable form of curcumin showed significant benefits for memory and attention after 18 months in a small sample of subjects with mild memory complaints. A larger replication study with more subjects is needed to confirm these results. Although epidemiological studies have shown an association between consuming spicy Indian food and better brain health, many of the available turmeric and curcumin supplements may not be absorbed adequately unless taken with a meal that contains fats or oils. At present, there is not enough evidence to recommend taking supplements containing curcumin for brain health.

**Flavonoids and cocoa.** Flavonoids are antioxidants found in plant-based foods. They are part of a family of chemicals called polyphenols that also include resveratrol, which is found in both red wine and chocolate. Cocoa beans, which are used to make chocolate, are high in flavanols. Some research has found that cocoa may increase healthy blood flow to the brain. Supplements containing cocoa are marketed for improving memory, focus, and cognitive performance. A few small studies funded by the industry have found that cocoa and cocoa flavanols might slightly improve attention and processing speed, but most aspects of thinking skills are unaffected. At present, there is not enough evidence to recommend taking supplements containing cocoa or flavanols or resveratrol for brain health. For more information about flavanols, see Brain Food: [GCBH Recommendations on Nourishing Your Brain Health](#).

**Ginkgo biloba.** Leaves from the ginkgo biloba tree have been used in Chinese medicine for centuries to treat problems with the heart, lungs and brain. Ginkgo is often taken as an herbal supplement. A study with more than 3,000 people over six years found that the supplement had no effect preventing Alzheimer’s disease, dementia or mild cognitive impairment. There is not enough evidence to recommend taking ginkgo biloba supplements to improve memory, protect the brain or reduce the risk of Alzheimer’s disease.

**Huperzine-A.** Huperzine-A is a naturally occurring substance found in the extracts of firmoss plants. It has been used in China for the treatment of swelling, fever and blood disorders. It may increase the levels of some

neurotransmitters in the brain and has been studied as a treatment for Alzheimer’s disease, but the studies have been small and inconclusive. There is not enough evidence to recommend taking a huperzine-A supplement for treatment of Alzheimer’s disease or memory problems, or for protecting aging brains.

**Medium-chain triglycerides (coconut oil).** Medium-chain triglycerides are a type of dietary fat that is especially high in coconut oil. They may be taken as a supplement, and coconut oil can be used for cooking. The body quickly converts medium-chain triglycerides into ketones, which can be used by the brain as an energy source. A few studies in rodents bred to develop Alzheimer’s disease showed cognitive benefit in the animals that received multi-chain triglycerides. There have been a few small studies of medium-chain triglycerides in humans, but the effects on cognition have been small; there is no evidence that they can prevent dementia or protect the brain in humans. Overall, there is not enough evidence to recommend taking supplements with medium-chain triglycerides or cooking with coconut oil for brain health. Indeed, consumers should be aware of the high fat content in coconut oil and may want to limit intake.

**Melatonin.** Melatonin is a hormone that plays an important role in sleep. The GCBH concluded in a previous report on [sleep and brain health](#) that sleep is vital to brain health, including cognitive function. Melatonin release in humans changes according to the time of day. Most people have higher levels of melatonin in the evening and lower levels in the morning. Supplements with melatonin have been studied in relation to sleep disorders, insomnia and jet lag, as well as for people who work night shifts. It has been studied for sleep and memory problems in people with Alzheimer’s disease and other forms of dementia. A number of studies have found that melatonin can improve the length of time needed to fall asleep, total sleep time and overall sleep quality in people with sleep disorders. One 2007 study in people with insomnia age 55 and older found that prolonged-release melatonin improved the quality of sleep and morning alertness. Although there have been a number of good studies about melatonin and sleep disorders, questions remain about how much to take, when to take it and long-term safety. Melatonin may modestly improve sleep, and sleep is important for brain health. Melatonin may have benefits for some, but the scientific evidence on its effectiveness for brain health is inconclusive. Those who are chronically bad sleepers should talk to their health care provider about getting help. Be aware that one study in

which extended-release melatonin was given along with the sleep medication Ambien found it exacerbated Ambien's negative effect on cognitive performance for several hours. For more detailed information about sleep and brain health, see the GCBH report "[The Brain-Sleep Connection](#)." We do not recommend using melatonin if you have dementia or mild cognitive impairment because of increased risk of falls and other adverse events, and there is insufficient evidence to recommend it for others.

**Nicotinamide riboside.** Nicotinamide riboside is a form of niacin (vitamin B3) that can be converted to the essential coenzyme NAD+. Research suggests that the level of this coenzyme decreases as we age. No studies have confirmed benefits of nicotinamide riboside in humans, although several trials are underway. There is not enough evidence for recommending the use of a nicotinamide riboside supplement for brain function, for dementia prevention or for Alzheimer's disease.

**Omega-3 fatty acids and fish oil.** Omega-3 fatty acids make up an important part of the membranes that surround each cell in your body. The three main omega-3 fatty acids are alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). ALA is an essential fatty acid; the body converts some ALA into EPA and DHA. Your body cannot make these fatty acids, so you must get them from the foods you eat. DHA is a building block of the brain. ALA is found mainly in plant oils such as flaxseed, soybean and canola oils, as well as nuts and seeds. DHA and EPA are found mainly in fish and other seafood. Fatty cold-water fish such as salmon, mackerel, tuna, herring and sardines are especially rich in DHA.

There have been numerous studies about omega-3 fatty acids and health including studies focused on heart health, rheumatoid arthritis and brain health, including depression. Research has found that people who eat more seafood have a lower risk of a decline in memory and thinking skills, including Alzheimer's disease. Therefore, the GCBH previously recommended the consumption of fish for protecting brain health. For more details, see [Brain Food: GCBH Recommendations on Nourishing Your Brain Health](#).

Omega-3 supplements, however, have not been found to reduce the risk of Alzheimer's disease. A few small studies have found that DHA supplements may benefit people with mild cognitive impairment, a condition that sometimes, but not always, leads to Alzheimer's disease. Additionally, there is evidence that the use of omega-3 supplements is effective in the treatment of older people with mild to moderate

depression, and that women with low levels of omega-3 tend to have higher rates of depression with more severe symptoms. Levels of omega-3 may be affected by many factors, including fish consumption, and some research has found that those who have low levels of DHA may benefit from supplements. However, the weight of the existing evidence does not sufficiently demonstrate benefit, and we do not recommend omega-3 supplements for brain health. If you can't or don't eat fish, ask your health care provider about whether you should take a supplement containing DHA and EPA.

Omega-3 supplements are made of fish oil, krill or algae and are offered in a wide range of doses and forms. Independent labs have found enormous variation in the content and the quality of various omega-3 supplements on the market. Omega-3 supplements can increase the risk of internal bleeding for those with bleeding disorders or for those who are taking medications that keep blood from clotting, such as warfarin (Coumadin), so make sure you talk to your health care provider about possible interactions between omega-3 supplements and medications. The 2019 AARP survey showed that 20 percent of Americans 50 and older are taking an omega-3 supplement.

NOTE: Experts have not established recommended amounts for omega-3 fatty acids, except for ALA. Average daily recommended amounts for ALA are listed below in grams (g).

LIFE STAGE	RECOMMENDED AMOUNT OF ALA
Men	1.6 g
Women	1.1 g

Source: *Food and Nutrition Board of the National Academy of Sciences, Engineering, and Medicine.*

**Phosphatidylserine.** Phosphatidylserine is a chemical in the body required to keep nerve cells healthy. It is important for sending and protecting messages in the brain. Although a few small studies found some benefit, larger studies have not confirmed that the supplement helps prevent cognitive decline or improve memory. There is not enough evidence for recommending the use of phosphatidylserine for brain health, mental functioning, or prevention or treatment of Alzheimer's disease.

### Safety and efficacy of dietary supplements

The steady rise of dietary supplement consumption across the world underscores the need for a closer examination of safety and issues surrounding this industry. In the United States, all prescription and nonprescription medications are subject to strict premarket regulation by the FDA. Dietary

supplements introduced to the market do not have to adhere to the same strict safety and efficacy requirements as medications. Similar regulatory bodies and regulatory schemes are in place in other countries or regions of the world.

Moreover, in the United States, while both the FDA and the FTC require that dietary supplement companies have scientific support for claims about the efficacy of their products, neither agency requires premarket approval of supplement claims. In general, dietary supplements are not considered medications, and therefore they are not subject to rigorous levels of premarket regulatory review. The health claims of dietary supplement manufacturers are generally not reviewed or approved by government agencies before the product goes on the market. In other words, dietary supplements are not approved for safety, efficacy or the truth of their claims by either the FDA or the FTC before they are sold.

The United States is the largest market in the world for dietary supplements, but many American consumers are not aware of the differences in how dietary supplements and medications are regulated. Consumers often incorrectly presume that the same rigor that is applied to drugs is also applied to supplements. In order for a new drug to be approved by the FDA, it must be rigorously tested for safety and efficacy through a three-phase approval process that typically takes more than a decade and costs millions of dollars. After it is on the market, the medication must be monitored for adverse effects. Even over-the-counter products and medications, such as aspirin and antiperspirant deodorant, must have evidence on file that they are safe and effective and have “Drug Fact” panels on their labels. But for dietary supplements, the requirements for labeling and reporting adverse events are not as extensive as they are for medical products.

In contrast to medical drugs, as a result of the 1994 Dietary Health and Education Act (DSHEA), the FDA does not require dietary supplements to be tested for safety or efficacy before being sold. There are some limited premarket requirements regarding safety notifications for new ingredients. Federal and state government agencies are authorized to take action against products that come on the market and break the law, but the burden is on the agency to identify and prove the violation. Dietary supplements in the United States have “Supplement Facts” panels on their labels, accompanied by a disclaimer that their claims and statements have not been evaluated by the FDA. Also worth noting is that no government agency is responsible for doing premarket evaluations to ensure that the ingredients in the supplements

match what their label claims. For additional information, see the comparison chart below: “Overview of the differences between drugs and dietary supplement classifications in the United States.”

### **Type and degree of regulation of dietary supplements vary widely by country**

In general, the regulation of dietary supplements is governed by individual countries’ laws, each of which has its own requirements, with the notable exception of the European Union (EU). The EU has regulations in place that cover all EU countries, and are in addition to the individual EU countries’ regulations. It is beyond the scope of this report to detail supplement regulations in each of these countries. But to give the reader a sense of the variation in regulation as well as the relatively lax standards of review for supplements compared to medications, we selected a few regions where supplements are relatively common and members of the GCBH expert panel live and work.

In the EU, supplements are regulated as foods by the European Food Safety Authority (EFSA). Between 2005 and 2009, EFSA conducted an assessment of substances that can be used as sources of vitamins and minerals in food supplements. The assessment includes the evaluation of safety and the effectiveness with which the mineral or vitamin is released into the body, sometimes called “bioavailability from the source.” Companies that wish to market a nutrient not included in the permitted list must apply to the European Commission for approval. EFSA then creates a scientific opinion about the nutrient. If a substance does not have a history of safe use in the EU before 1997, EFSA is requested to provide a scientific opinion on its safety. The European Commission reviews and updates the lists of nutrients that may be used in food supplements. Member countries of the EU also have separate regulations. For example, Italy—which has the largest market for dietary supplements in Europe—has a national list of food supplements. In the United Kingdom most products described as food supplements (such as vitamins, minerals, or amino acids) are regulated as foods and subject to the provisions of general food law such as the Food Safety Act. If a company sells food supplements, it must register as a food business operator (FBO) with its local authority.

Just as in the United States, differences in health care regulation may not always be apparent to consumers and health care providers across Europe. Melatonin, for example, is prohibited in the Czech Republic, but its sale is allowed in many other European countries. For traditional herbal medicines in the European Union, there is no requirement to scientifically substantiate that the product is effective. It is

enough to show that the product has been used for at least 30 years, at least 15 of which have been in the European Union.

China has one of the world's largest supplements markets, second only to the United States. In China, dietary supplements are regulated as "health foods." In 2015, the country's Food Safety Law changed the regulation of health foods. Health foods that have ingredients outside an approved list must be registered with the government. Labels are prohibited from promising preventive or therapeutic benefits.

Traditional Chinese medicine practitioners have used herbal medications for more than 4,000 years. Herbal medicines used in traditional Chinese medicine are sometimes marketed as supplements in the United States and Europe. However, in China, these herbal medications are regulated separately from vitamin and mineral supplements. Over the past few years the country has been actively promoting traditional Chinese medicine. Herbal medicines are prescribed by registered medicine practitioners for specific diseases. The herbal medications are not required to undergo clinical trials. There have been reports of Chinese herbal products that have been contaminated with toxins, heavy metals or drugs and that do not contain the listed ingredients, according to the U.S. National Center for Complementary and Integrative Health. Some herbs used in Chinese medicine can have serious side effects or drug interactions, or can be unsafe for people with certain medical conditions.

### **Problems with quality and quantity of ingredients in dietary supplements**

In addition to the lack of evidence for the effectiveness of brain health supplements and the potential for impurities, consumers may not be getting what they believe they are paying for. Supplements may have too much, too little or, in some cases, none of the ingredient they think they are buying. Undeclared ingredients may even be dangerous.

Dietary supplements are manufactured through processes that are less regulated than those for prescription medications. The manufacturing process can introduce substances to which people are allergic (e.g., gluten and nuts) or that they may wish to avoid (e.g., trans fat or pesticides). Supplement manufacturers that follow Current Good Manufacturing Practices (CGMP) can provide effective quality control for their products. But there are thousands of supplement manufacturers in the United States and the FDA does not review all of them. For those it does review, the FDA often finds irregularities. One example of unknown ingredients in supplements causing serious health problems

was OxyElite Pro, described on its product label as containing "proprietary blends of plant-derived extracts." In 2013 OxyElite Pro was taken for weight loss or muscle building. Advertised as a fat-burning supplement and sold nationwide, this dietary supplement was pulled from shelves after officials linked it to cases of liver failure and acute hepatitis in dozens of people in Hawaii. Two people required liver transplants and one died after taking the supplement. The cause of liver toxicity was not identified, but contamination was suspected.

A 2013 United States government report found that from 2008 to 2011, the FDA received more than 6,000 reports of health problems due to dietary supplements, including 92 deaths and more than 1,000 serious illnesses or injuries. The report pointed out that claims of adverse events don't prove that the supplements caused the reported health problems. Nevertheless, the problems were suspected to be caused by drug interactions, actions of the supplements themselves, impurities/contaminants found in the supplements, or combinations of all three. The FDA and independent testers of supplements have found dangerous fungi, pesticides, environmental pollutants and heavy metals in some products. Between 2007 and 2016, the FDA found more than 700 dietary supplements contained prescription drugs, including steroids, antidepressants, sildenafil (Viagra and generics) and drugs that have been banned by the FDA. Most of these products were marketed for sexual enhancement, weight loss or muscle building.

In 2015 the New York Attorney General's office found that four popular herbal supplements did not contain the plant advertised and asked GNC, Target, Walgreens, and Walmart to stop selling the products. Since then, although the accuracy of the testing was challenged, a number of manufacturers of herbal products have agreed to improve quality control; however, problems persist. In late 2018, the GAO published a report on three products they tested that were marketed as memory supplements. These three supplements were selected from a list of highly advertised products in the United States because they were popular and readily available through common retailers. None of the three labels accurately reflected the content of the pills. One contained none of the product's stated ingredients, one contained less than the quantity of the ingredient stated on the label, and the third contained more than the quantity stated. The GAO was careful to point out: "The results of this testing are limited to the highly advertised supplement samples that GAO had tested and are not projectable to the entire universe of memory supplements." Nevertheless,

unfortunately, labeling inaccuracies are relatively common in the supplement industry.

In February 2019, the FDA announced new efforts to strengthen regulation of the dietary supplements industry through modernizing and reforming its oversight. As part of a joint enforcement initiative with the FTC, the FDA sent 12 warning letters and five advisory letters to companies that it said were selling more than 58 products that contained unapproved drugs or were marketed with illegal claims that the product would prevent, treat or cure Alzheimer’s disease or other serious illnesses.

The 2019 AARP Brain Health and Dietary Supplements Survey revealed the majority of Americans are concerned

Topic of concern relating to dietary supplements	Percent of adults age 50+ extremely/very concerned	Percent of adults age 50+ somewhat concerned
Purity	46	30
Safety	47	24
Effectiveness	47	29

about the purity, safety and effectiveness of dietary supplements.

Seventy-three percent of respondents were also concerned about the thoroughness of government review of dietary supplements. (42 percent are extremely/very concerned and 31 percent are somewhat concerned.)

**Third party verification**

In response to the variability and uncertainty associated with supplements, several independent organizations provide testing and other services to manufacturers and suppliers to ensure the quality and safety of the products they sell and to help consumers in identifying quality products. USP and NSF both award easily identifiable seals to products available in stores. ConsumerLab.com tests products to verify they contain the ingredients reported and makes this information available online through a subscription service. Programs that demonstrate a supplement’s identity, potency, purity, and performance are useful for health care practitioners and consumers to ensure that the supplements meet strict

standards, follow good manufacturing practices, and will dissolve and be absorbed in the body as expected.

**Evaluating supplement health claims and marketing materials**

In the United States, the FDA and FTC share authority over marketing claims for dietary supplements, including supplements marketed for memory or brain health. Under a longstanding liaison agreement, the FTC has primary authority for claims appearing in advertising, including TV, radio, print, the Internet and social media, and the FDA has primary authority for claims appearing in labeling. The FTC Act requires that advertising be truthful and not misleading and that advertisers possess adequate substantiation for claims before an ad is disseminated. Claims about the efficacy of supplements for memory or brain health, including dementia and Alzheimer’s-related claims, require support by competent and reliable scientific evidence. The FTC does not preapprove such claims, but does bring enforcement actions when it determines claims are not adequately substantiated.

Under FDA law, dietary supplement companies are prohibited from making any claim that a supplement can treat, prevent or cure any disease, including dementia or Alzheimer’s disease. Such disease claims render the supplement an unapproved and/or misbranded drug. Supplement marketers wishing to make certain health claims, such as that their product can reduce the risk of dementia, must notify the agency of the claim and first petition the FDA for authorization of the claim before it can be placed on the product label. Claims discussing normal structure or function of the body, such as maintaining memory or healthy brain function, do not undergo premarket approval. Like the FTC, FDA regulation does require that a marketer possess adequate substantiation for these claims, in the form of competent and reliable scientific evidence, before the claims appear in labeling. However, manufacturers are not required to submit such evidence, and the FDA does not review the substantiation.

As you will see below, numerous supplement manufacturers have been either saying or implying in their marketing material that their supplement can improve or treat cognitive decline or improve brain health. Some, as the FDA recently alleges with respect to several supplements below, are actually claiming their product treats Alzheimer’s disease. The supplement labels are permitted to say they “help maintain” or “support” brain health. But the labels or other marketing material may also contain language that tends to mislead or confuse consumers into believing the product is

safe and effective for the intended use. “Clinically studied” does not mean the same thing as proven safe and effective for the purpose by rigorous, well-designed scientific studies in humans. “Natural” does not always mean safe. “Statistically significant” doesn’t establish that it is likely to or actually will positively affect human health.

The claims below in italics are taken directly from marketing material of dietary supplements currently sold in the United States that are purporting to support or enhance brain health. The language was selected to provide consumers with examples of companies making it sound like their product could improve brain health. The five examples at the end of the list are taken from the warning letters sent to supplement companies by the FDA for products specifically claiming to treat Alzheimer’s disease in February 2019.

The Global Council on Brain Health does not believe sufficient evidence exists to support any of the product claims below. None of the products making the claims below are recommended by the GCBH for the purpose of helping, maintaining or improving brain health; preventing cognitive decline; preventing dementia; or slowing, improving or stopping the symptoms of any neurological disease such as Alzheimer’s.

*A dietary supplement that has been clinically shown to help with mild memory problems associated with aging.*

*Clinically shown to be safe and support memory and brain function.*

*Clinically proven natural ingredients.*

*Clinically shown to significantly increase key levels of key neuroproteins.*

*Supports neurotransmitter development to promote a feeling of mental sharpness.*

*Helps your brain maintain healthy neurons to support learning and recall.*

*13 scientifically proven nutrients for a healthier brain.*

*Keeps your mind sharp and memory strong with an ingredient that’s clinically shown to improve memory and recall in healthy adults. It’s powered by the #1 most clinically studied ingredient for memory among leading brain health supplements.*

*Has shown statistically significant improvements in memory and recall in as little as 4 weeks when taken as directed.*

*To Improve and Boost Brain Power, Mind, Concentration & Energy For Healthy Brain Function & Support*

*Enhance memory, concentration, focus, mental clarity and learning abilities.*

*Designed to help improve memory while increasing focus and concentration.*

*Comprehensive blend of vitamins, amino acids, and herbal extracts that support the brain’s structure and function to deliver amazing improvements in memory and concentration!*

*Give your brain the compounds it needs to help keep your mind bright, clever and strong.*

*Help lessen the frequency of episodes of forgetfulness and brain fog.*

*Improve your ability to retain and recall various kinds of information.*

*For Cognitive Health, Memory Improvement, Memory Enhancement*

*These key nutrients have a powerful effect at reducing the inflammatory fires that destroy our brain tissue.*

*It aids in improving connectivity between neurons and brain cells. It’s shown positive effects for improving memory, reaction times, and clarity of thought.*

*A highly esteemed Ayurvedic herb with a history of use that goes back over 3,000 years. Legend has it that it was used by ancient scholars to memorize lengthy hymns and scriptures.*

*It’s needed for over 300 metabolic functions and has profound effects on brain and mental health.*

**Examples of claims to treat Alzheimer’s disease continued on the next page.**

The following examples are claims made by several companies that sell products in the United States that have been advertised as treatments for Alzheimer's disease. These claims prompted the FDA and the FTC to issue warning letters in February 2019 to the manufacturers stating that their claims make these products "new drugs" within the meaning of the Food Drug and Cosmetic Act, a classification that requires a product to receive prior approval by the FDA before it can be sold. The letters also warned that the efficacy claims for these products were unsubstantiated, in violation of the FTC Act. The agencies cited these claims as examples of violations of law:

*Useful for patients with post stroke, vascular dementia, suspected Alzheimers [sic] disease, Parkinsons [sic], transient ischemic attack (TIA).* Warning letter sent for unsubstantiated claim available at [fda.gov/ICECI/EnforcementActions/WarningLetters/ucm630531.htm](https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm630531.htm)

*Recent research suggests that many 'young' people in their 40s are exhibiting early symptoms of Alzheimer's disease. This should be a wake-up call for everyone. Research also suggests that the proline-rich polypeptides in bovine colostrum (CDPs) may help in the fight against Alzheimer's disease and other brain diseases that involve cognitive decline.* Warning letter sent for unsubstantiated claim available at [fda.gov/ICECI/EnforcementActions/WarningLetters/ucm630558.htm](https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm630558.htm)

*Prescription drug for Alzheimer's/Parkinson's.* Warning letter sent for unsubstantiated claim available at [fda.gov/ICECI/EnforcementActions/WarningLetters/ucm630486.htm](https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm630486.htm)

*Supplementation shown to reduce risk of Alzheimer's Disease.* Warning letter sent for unsubstantiated claim available at [fda.gov/ICECI/EnforcementActions/WarningLetters/ucm630486.htm](https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm630486.htm)

*These following steps are crucial to preventing Alzheimer's disease and so effective, they could reverse the momentum of Alzheimer's.* Warning letter sent for unsubstantiated claim available at [fda.gov/ICECI/EnforcementActions/WarningLetters/ucm630570.htm](https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm630570.htm)

The FTC press release, with links to specific letters sent by FTC is available here: [ftc.gov/news-events/blogs/business-blog/2019/02/ftc-fda-warning-letters-target-treatment-claims-alzheimers](https://www.ftc.gov/news-events/blogs/business-blog/2019/02/ftc-fda-warning-letters-target-treatment-claims-alzheimers)

Consumers should approach brain health claims made on supplement labels and marketing materials with skepticism. Supplement manufacturers' claims may describe how an ingredient might solve a nutritional deficiency, improve the structure or function of a part of the brain, or promote well-being. But supplement manufacturers are not permitted to claim their product treats, cures or prevents a disease without proving it through clinical trials before these products are introduced to the market.

## Overview of the differences between drugs and dietary supplement classifications in the United States

Drugs	Dietary Supplements
In general, the FDA considers drugs to be unsafe until proven safe.	Dietary supplements are defined as a category of food and are therefore subject to different regulations than drugs. Dietary supplements are considered safe until proven otherwise.
Clinical trials in human volunteers are the gold-standard for proving safety. The drug development pipeline involves Phase I, II and III clinical trials before drugs are introduced to the market.	Dietary supplements cannot include any ingredients that may pose a significant or unreasonable risk of illness or injury, but it is up to the FDA to find and prove a violation. Safety does not have to be proven supported by clinical trials before supplements can be sold.
Clinical trials in human volunteers are the gold-standard for proving efficacy. The drug development pipeline involves Phase I, II and III clinical trials before drugs are introduced to the market.	Unlike drug marketers, dietary supplement marketers are not required to submit scientific support for efficacy claims to obtain premarket approval. While both the FDA and FTC do require that such claims be supported by competent and reliable scientific evidence, they don't verify the claims.
Clinical trials must be conducted on all drugs, even those sold without a prescription (i.e., over the counter).	If an ingredient in a dietary ingredient is "new," (meaning it was introduced after 1994) the manufacturer is supposed to first provide the FDA with evidence as to why the ingredient is reasonably expected to be safe. However, there is a low overall compliance rate and manufacturers are not required to test new ingredients in dietary supplements for safety or effectiveness in clinical trials.
Once the FDA approves a drug, it must be manufactured under carefully monitored conditions.	The FDA has established current good manufacturing practice requirements (cGMPs) for dietary supplements. However, the agency does not monitor manufacturing processes except when the facility is periodically inspected. The FDA inspection rate is low compared to the number of facilities and rate of noncompliance is high.
Dosage and schedule must be clearly stated on the product label.	Dietary supplement labels must include name and location information for the manufacturer or distributor as well as serving size and percent of recommended daily value, if applicable. Generally the quantity of ingredients is to be declared on the label, but not in a proprietary blend of ingredients.
Package information must include: conditions the drug has been clinically proven to treat, known side effects, contraindications (special conditions under which using the drug carries too much risk for patients with particular health considerations), as well as unsafe interactions with other drugs.	Dietary supplements generally do not need to provide package information listing potential side effects, adverse effects or contraindications for certain people or (with few exceptions) list these on the label. Some products do this voluntarily.
Drugs are monitored once on the market and there is follow-up by the FDA in cases where adverse effects are reported by clinicians or patients resulting from the drug.	Dietary supplements are not routinely monitored after they come on the market, but people can report problems to the FDA if they think a supplement caused a serious reaction or illness. Supplements are judged to be unsafe only after they cause harm. Firms are supposed to report serious adverse events to the FDA.

*Note: information from the American Cancer Society website provides additional useful information and was a helpful source to us in constructing this table:*

[cancer.org/treatment/treatments-and-side-effects/complementary-and-alternative-medicine/dietary-supplements/fda-regulations.html](https://www.cancer.org/treatment/treatments-and-side-effects/complementary-and-alternative-medicine/dietary-supplements/fda-regulations.html).

# KNOWLEDGE GAPS: WHERE MORE RESEARCH IS NEEDED

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Research can help solidify the link between micronutrient deficiency, supplementation and brain health, although research in this area can be more challenging than other approaches to improve brain health. Because micronutrient levels differ between diets around the world, it can be difficult to determine whether people's baseline health is comparable when researchers examine people who take or do not take supplements. Micronutrient levels also are not routinely measured in observational studies, and it is possible that some people absorb certain supplement levels better than others. When supplement levels are not measured in standardized blood tests, researchers' interpretations can be biased.

## **More quality studies in humans that focus on cognitive effect**

Simply because there is research showing effect of a substance in the lab, at the cellular level, or in animal trials, this does not mean it will translate into human benefit. Sometimes supplement manufacturers rely on preliminary or early scientific enquiry, or general scientific principles or evidence of other potential health benefits, to support their claims making or implying a brain health benefit. To truly understand how supplement use affects long-term brain health, we need more large, long-term high-quality randomized controlled trials in humans during which one group receives a placebo—a substance that has no effective compound—and another group gets the supplement. These trials should also be “double-blind,” so that neither the researchers nor those in the study know whether they are receiving the supplement or the placebo. The studies' outcomes should not be influenced by the supplement manufacturers. Unfortunately, there are very few high-quality human studies completed on the vast array of dietary supplements compared with the number of products that are being sold or taken for brain health.

## **Measure nutrient levels with blood samples**

Much of the information we have about how supplement use relates to cognition has come from observational studies designed to study other aspects of aging and brain health. Often these studies have relied on self-reported histories of supplement intake, so supplement-use history is not recorded with as much care as is typical for prescription-medication use in clinical trials. People who use one supplement are also more likely to use other supplements, have healthier lifestyles and have greater financial resources, which could be responsible for the differences in outcomes for people being tested. Thus,

establishing a link between better brain health and regular use of a particular supplement without accounting for these well-known traits of supplement users can lead to incorrect and misleading conclusions. A first step in remedying this is to come up with a standard approach in population studies to record and quantify supplement use. As mentioned earlier in the document, information on the supplement label often does not accurately reflect the dosage and purity of each supplement. People can also exaggerate or hide their supplement use. Thus, for maximal reliability, all studies related to supplementation should have stored blood samples to measure actual nutrient levels in each person.

## **Better identify those susceptible to micronutrient deficiencies**

Some people have genetic disorders that prevent the efficient uptake of micronutrients from their diet—either from the gut to the blood or from the blood to the brain. When these conditions are severe, people can develop neurological symptoms when they are children. However, there is insufficient understanding concerning people who have milder cases of genetic abnormalities, or people who develop absorption issues because of medical or other reasons (e.g., irritable bowel disease, bariatric surgery). Physicians can sometimes uncover nutritional issues after people develop symptoms, but there is a need to better understand what proportion of the population is at risk for chronic deficiencies. It is also not clear if the deficiencies' negative impact on brain health is reversible (partially or completely) and, if so, how the supplementation needs to take place (dose, route, frequency). It is possible that including people with these chronic deficiencies in studies may skew the results. It's important to study people who don't have chronic nutritional deficiencies to see if a supplement improves long-term brain health in the general population.

## **Study supplement use in those with nutritional deficiencies**

Even when a nutritional deficiency may be causing neurological symptoms, there are few agreements between physicians, scientists and other types of health practitioners on when supplementation should begin. For example, providers can start people on vitamin B12 supplementation when B12 level in the blood is lower than the normal range, when it is in the bottom half of the normal range, or when another marker is elevated (e.g., homocysteine, which can result from chronic B12 deficiency). Supplements can also be delivered by taking a pill,

injecting it into the muscle or infusing it into the vein. More studies are needed to better identify who may benefit from supplementation when a micronutrient deficiency is clearly suspected.

### **Measure how much of the nutrient gets into the brain**

When researchers study prescription drugs that have an effect on the brain, a key experiment that they perform is measuring how much of the drug taken (orally or through other routes) gets into the brain. Not all substances taken by mouth survive the strong stomach acid, and not all substances that persist beyond the stomach get absorbed into the blood. Even after absorption into the blood, the liver can further break down the substance, and the blood-brain barrier—the natural gatekeeper of the brain—may keep out what is left. Usually it is not known how much—if any—of the supplement people take gets into the brain. When a nutrient is absorbed into the blood but not into the brain, people can still experience undesirable side effects (e.g., nausea, dizziness). Therefore, even when people feel a difference (good or bad) after taking a supplement, there is no guarantee that it is reaching the brain. So a key step in using science to support any supplement's benefit on brain health would be to study how much of each nutrient gets to the brain.

### **Study the effect of supplements on those with Alzheimer's disease**

When healthy people are considering the use of these supplements, the potential harm is weighed heavily against the questionable benefits. However, when people have incurable diseases such as Alzheimer's disease, the long-term harm may be less relevant if there are true benefits in the short term. Many of the available supplement-related studies in people with dementia were performed before we could identify people with Alzheimer's disease with high confidence, or lump together people with Alzheimer's disease and other similar (but not the same) disorders. With the availability of biomarkers capable of differentiating Alzheimer's disease from other types of diseases that can mimic the symptoms of Alzheimer's disease, future clinical trials on the efficacy of supplements should include the use of these biomarkers.

### **Systematic review of the available literature**

Increasingly, clinical decision-making is guided by the use of systematic review tools, including meta-analysis, to properly evaluate, analyze and synthesize the available data. As more data accumulate to address the possible role of dietary supplements on brain health, we should insist on applying these tools in making decisions on patient management.

## CONCLUSION

There is no convincing evidence to recommend dietary supplements for brain health in healthy older adults. The consensus statements and recommendations above are based on the current state of science as of May 2019. Supplements have not been demonstrated to delay the onset of dementia, nor can they prevent, treat or reverse Alzheimer's disease or other neurological diseases that cause dementia. For most people, the best way to get your nutrients for brain health is from a healthy diet. Unless your health care provider has identified that you have a specific nutrient deficiency, there is not sufficient data to justify taking any dietary supplement for brain health. The GCBH does not endorse any ingredient, product or supplement formulation specifically sold for brain health. Because no government agency determines dietary supplements are safe or effective before they are sold, consumers should approach supplements claiming to improve or boost brain function with skepticism. Because dietary supplements can be sold without a government agency first determining that they are safe and effective before they are sold, consumers should also be aware that in addition to being a waste of money, some supplements could physically harm them.

Despite claims to the contrary, brain health supplements have not been established to maintain thinking skills or improve brain function. However, there are many other lifestyle habits such as getting enough sleep, exercising regularly, eating a healthy diet, staying mentally active and being socially engaged that are recommended by the council. For evidenced-based strategies on what you can do to help maintain your brain health as you age, see the council's other reports, available at our website: [GlobalCouncilonBrainHealth.org](http://GlobalCouncilonBrainHealth.org).

## LIST OF APPENDICES

1. Participants, with participants' and liaisons' list of additional resources
2. Glossary
3. Discussion questions framing the deliberations
4. Differences, strengths and limitations of two study types in humans
5. Disclosure statements of potential conflicts of interest
6. Funding
7. Selected references

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## Participants' and Liaisons' List of Additional Resources

Cognitive Vitality:  
[alzdiscovery.org/cognitive-vitality](http://alzdiscovery.org/cognitive-vitality)

ConsumerLab.com:  
[consumerlab.com](http://consumerlab.com)

Description of EU Regulations:  
[efsa.europa.eu/en/topics/topic/  
food-supplements](http://efsa.europa.eu/en/topics/topic/food-supplements)

Description of UK Regulations:  
[food.gov.uk/sites/default/  
files/media/document/  
foodsupsupplementsenglish\\_o.pdf](http://food.gov.uk/sites/default/files/media/document/foodsupsupplementsenglish_o.pdf)

Federal Trade Commission—  
Information on how to report  
how to report a concern about  
a supplement: [consumer.ftc.  
gov/blog/2017/07/dietary-  
supplement-concerns-tell-ftc-  
and-fda](http://consumer.ftc.gov/blog/2017/07/dietary-supplement-concerns-tell-ftc-and-fda)

FTC press release following  
recent enforcement actions: [ftc.  
gov/news-events/blogs/business-  
blog/2019/02/ftc-fda-warning-  
letters-target-treatment-claims-  
alzheimers](http://ftc.gov/news-events/blogs/business-blog/2019/02/ftc-fda-warning-letters-target-treatment-claims-alzheimers)

Office of Dietary Supplements:  
[ods.od.nih.gov](http://ods.od.nih.gov)

United States Food and Drug  
Administration: [fda.gov](http://fda.gov)

United States Government  
Accountability Office report to  
Senators McCaskill and Casey,  
October 18, 2018: [https://www.  
gao.gov/assets/700/695049.pdf](https://www.gao.gov/assets/700/695049.pdf)

United States Pharmacopeia:  
[quality-supplements.org](http://quality-supplements.org)

\*Participation in this activity by these individuals does not necessarily represent the official viewpoint of the U.S. Department of Health and Human Services, the National Institutes of Health, the National Institute on Aging, the Food and Drug Administration or the Federal Trade Commission.

## 2. GLOSSARY

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The glossary highlights how the GCBH used these terms within the context of their discussions and in this document.

**Botanical.** Having to do with plants or plant parts, or dietary supplement products made from plants..

**Brain health.** A state of having good underlying neural mechanisms to support high functioning mental processes of cognition that support well-being.

**Cognitive decline.** The Institute of Medicine (IOM) in 2015 defined a similar term, cognitive aging, as the lifelong process of gradual and ongoing, yet highly variable, change in cognitive functions that occur as people get older. Cognitive decline is a term used by the experts to describe losing cognitive abilities over time as people age absent a specific disease or condition.

**Confounder.** A situation in which the effect or association between an exposure and outcome is distorted by the presence of another variable.

**Daily Value (DV).** A term used on a food or dietary supplement label that tells you how much of a particular nutrient (such as calcium) one serving of the food or supplement provides. DVs are given as percentages and help you compare one product with another. For example, a food that lists 40% DV for calcium would provide much more calcium than another food that lists 10% DV for calcium. For each nutrient, there is one DV for all people aged 4 years and older. DVs are established by the U.S. Food and Drug Administration.

**Deficiency.** An amount that is not enough; a shortage or insufficient quantity.

**Dementia.** Dementia isn't a specific disease. Instead, dementia describes a group of symptoms related to memory, thinking and social abilities and affecting them severely enough to interfere with independent daily functioning. Though dementia generally involves memory loss, memory loss has many different

causes. Alzheimer's disease is the most common cause of a dementia in older adults, but there are a number of types of dementia. Depending on the cause and type of dementia, some dementia symptoms can be reversed.

**Efficacy.** The ability, especially of a medicine or method, to produce the desired or intended result.

**Enzyme.** A protein that speeds up chemical reactions in the body.

**Epidemiological studies.** In these studies, which are observational in nature, scientists try to establish a link between lifestyle activities over time (e.g., education) and long-term outcomes (brain health with aging). They can be cross-sectional or longitudinal.

**Fortified.** When nutrients (such as vitamins and minerals) are added to a food product. For example, when calcium is added to orange juice, the orange juice is said to be "fortified with calcium". Similarly, many breakfast cereals are "fortified" with several vitamins and minerals.

**Ingredient.** In a dietary supplement, an ingredient is a component of the product, such as the main nutrient (vitamin, mineral, herb, amino acid, or enzyme) or any binder, color, filler flavor, or sweetener. In herbal supplements, the common name and Latin name (the genus and species) of the plant is given in the ingredient list. On a dietary supplement label, the ingredients are listed by weight, with the ingredient used in the largest amount first on the list and the ingredient used in the least amount at the end of the list.

**International unit.** IU. A measurement used to measure the activity of some vitamins and other biological substances (such as enzymes and hormones).

**Intervention.** Action taken to improve a situation, especially a medical disorder.

**Longitudinal studies.** In longitudinal research, scientists observe changes over an extended period of time to establish the time sequence in which things occur or the effect of a factor over time.

**Medical food.** A food which is formulated to be consumed or administered under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements are established by medical evaluation.

**Mineral.** In nutrition, an inorganic substance found in the earth that is required to maintain health.

**Nutrient.** A food or biochemical substance used by the body that must be supplied in adequate amounts from foods consumed. There are six classes of nutrients: water, proteins, carbohydrates, fats, minerals, and vitamins.

**Placebo.** A substance that is given to someone who is told that is the medicine, but it is not, given to compare the effect of the medicine when given to others.

**Purity.** Freedom from contamination.

**Quality control.** A system to ensure that consistency and uniformity are maintained in the manufacturing of a product.

**Randomized controlled trial (RCT).** In a typical randomized controlled trial, people are randomly selected to receive either the intervention or a control condition. In a double-blind RCT, both the participants and the researchers are unaware of (or "blinded" to) which person received the intervention until after the results are analyzed.

**Risk.** Risk is the chance or probability of a particular event happening in a group of people with similar characteristics or traits, compared with those not having that characteristic or trait. Making up an individual's overall risk of having

a condition is the cumulative effects of factors that increase the chance of developing the condition (risk factors) as well as factors that decrease the chance of developing the same condition (protective factors).

**Risk reduction.** Reducing risks for cognitive decline or impairment in the abilities to think, reason and remember means lowering your chances of experiencing loss in those abilities. A person's overall risk may also be reduced by increasing factors that protect against cognitive decline or dementia. Dementia (cognitive impairment due to Alzheimer's disease or another related disorder) is one condition, and age-related cognitive decline (the slowing of thinking and memory as one ages in the absence of a major brain disease) is another condition. When scientists study risk-reduction strategies for cognitive decline, they are looking for factors that can reduce the

risk of impairment to cognitive functions in the population in general. Therefore, some activity or intervention that reduces risk for a particular condition or disease means that a smaller proportion of people who engage in that activity are likely to have the condition or disease. However, risk reduction strategies are not the same as preventing any one individual from getting the condition or suffering from disease. For example, research has long shown that wearing a seatbelt reduces—but does not eliminate—the chance of injury among people who are involved in automobile accidents, and we nevertheless now recommend people wear seatbelts while they are driving.

**Standardization.** A process manufacturers may use to ensure batch-to-batch consistency of their products and to provide a measure of quality control. Dietary supplements are not

required to be standardized in the United States. Some manufacturers use the term incorrectly or to mean different things and the presence of the word "standardized" on a supplement label does not necessarily indicate a level of product quality.

**Supplement.** A product taken by mouth that contains a "dietary ingredient." Dietary ingredients include vitamins, minerals, amino acids, botanicals (including herbs) and enzymes, as well as other substances alone or in combination that can be used to supplement one's diet. Supplements come in many formulations, including pills, capsules, tablets, powders, food bars and liquids.

**Vitamin.** A nutrient that the body needs in small amounts to function and maintain health. Examples are vitamins A, C, and E.

### 3. DISCUSSION QUESTIONS FRAMING THE DELIBERATIONS

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1. Background definitions
  - a. How does the GCBH define dietary supplements?
  - b. What are nutraceuticals?
  - c. What are functional foods?
  - d. What are medical foods?
2. Supplements marketed for brain health in healthy individuals at *any* age
  - a. Is there evidence that specific supplements (or supplement ingredients) can maintain brain health (e.g., prevent memory loss)? If so, which ones and in what formulations/doses?
  - b. Is there evidence that specific supplements or ingredients can lead to better brain health (i.e., help improve memory, reasoning, clarity of thought, attention and focus)? If so, which ones and in what formulations/doses?
  - c. Is there evidence that specific supplements or ingredients can boost intelligence (often measured by IQ scores)? If so, which ones and in what formulations/doses?
  - d. Does the efficacy of supplements depend on how long they are taken (e.g., one year, five years)?
  - e. Are there any circumstances in/conditions for which consumers over 50 should consider taking vitamin or mineral products?
  - f. Does it make a difference whether people take multivitamins versus single vitamin/mineral supplements?
  - g. Does baseline nutritional status determine the efficacy of dietary supplements, particularly vitamins and minerals? For example, do vitamins work differently for those that are deficient?
3. Dietary supplements and neurodegenerative diseases, such as Alzheimer's
  - a. Have any specific supplements or supplement ingredients been proven to prevent the onset of neurodegenerative diseases? If so, which, and in what formulations/doses?
  - b. For individuals already experiencing memory loss, have any specific supplements or ingredients been shown to reverse the decline and help them to regain their memory capacity? If so, which, and in what formulations/doses?
4. General issues
  - a. What testing requirements are there for safety and efficacy before dietary supplements are sold? How is this different from OTC and pharmaceutical drugs? What do consumers need to know?
  - b. What issues should consumers be aware of regarding purity, composition or quality control?
  - c. What safety issues should consumers be aware of?
  - d. What efficacy issues should consumers be aware of?
  - e. What regulatory issues should consumers be aware of?
  - f. Many people take more than one supplement. What should people who take more than one supplement be aware of? (risks, interactions, dosage)
  - g. How can consumers choose a high-quality dietary supplement?
  - h. How can consumers learn about quality issues and health risks associated with dietary supplement products?
  - i. Are there any particular ingredients consumers should avoid or adulterants that they should be aware of? (Please keep answers constrained to ingredients most relevant to supplement products being marketed to people over age 50.)
5. What, if any, scientific evidence exists that shows the efficacy of the supplements and/or their ingredients commonly sold and taken by people for the purpose of maintaining or improving brain health or cognitive functions such as memory or reasoning?
6. What is the evidence for/against omega-3s in terms of health benefits for people over 50? Does taking omega-3 supplements offer the same benefits as eating fish? What specific concerns (e.g., difference between DHA and EPA, dosing, quality, sourcing) should consumers be aware of?
7. In general, does the form of intake (e.g., supplement pills, liquid, functional foods such as shakes) of dietary supplements matter?
8. Putting this all together, what message should we be sending to consumers over 50 about the possible health benefits, concerns and risks of dietary supplements being marketed to this age group? What questions should consumers ask themselves when considering marketing claims? How should consumers decide whether or not to take a product?

## 4. DIFFERENCES, STRENGTHS AND LIMITATIONS OF TWO STUDY TYPES IN HUMANS

	Epidemiological Studies	Randomized Controlled Trials
Purpose	To observe a group of people in their natural surroundings (often over extended periods of time), and to identify personal characteristics, behaviors and conditions that predict someone's chance of developing a condition or a disease.	To determine, in a controlled setting, whether implementing a change (in behavior, diet, medication, etc.) can definitively lead to a specific outcome. This compares those engaging in an activity with those not engaging in the activity.
Example	Researchers who survey and follow women living in Metropolis show that women who run weekly have fewer incidents of heart attack in their 60s.	Researchers at University Medical Center wish to recruit 500 women in their 60s to determine whether having them run weekly can reduce their chance of heart attack during the one year study compared to those who don't run.
Study duration	Years to decades	Weeks to months, sometimes years
Strengths	<ul style="list-style-type: none"> <li>• Usually larger number of people</li> <li>• Can take into account influences from many more factors and personal characteristics and disease states</li> <li>• Can assess many dose levels and durations of behavior</li> <li>• Can detect slow or cumulative changes over time</li> <li>• Where observational studies are representative of the population, they have greater external validity, which means that the findings can be applied to a wider range of people</li> </ul>	<ul style="list-style-type: none"> <li>• Helps to prove causal link and to better understand mechanisms</li> <li>• Randomization can eliminate many competing hypotheses as why the change actually happened (because confounding factors have an equal probability of occurring in all groups)</li> <li>• Can test whether different dose of the intervention (e.g., exercise frequency, drug dose) can lead to different outcomes</li> <li>• Uses detailed and objective measurements and assessments</li> </ul>
Limitations	<ul style="list-style-type: none"> <li>• Does not prove any specific causal link.</li> <li>• May not capture all characteristics that influence health.</li> <li>• Any characteristic may reflect another more important factor (e.g., people who take expensive medications may have better access to health care).</li> <li>• Selective drop-out of those less socially advantaged and less healthy.</li> <li>• Difficult to generalize from one region to another due to differences in diet, environment, health care, etc.</li> <li>• Often cannot collect detailed information due to the large numbers of participants and measures.</li> <li>• Expensive to set up and run, especially over long periods.</li> <li>• Some studies rely on self-reported behavior which may be inaccurate.</li> <li>• People who partake in a study to be followed for long periods of time might bias inclusion.</li> </ul>	<ul style="list-style-type: none"> <li>• Usually smaller number of people</li> <li>• While an RCT attempts to control for confounding factors, it may not capture all characteristics which influence health.</li> <li>• The study may be too limited in size or duration to detect subtle effects.</li> <li>• Difficult to test conditions which scientists cannot change (e.g., gender, genetics, past exposure)</li> <li>• Difficult to generalize from one region to another due to differences in diet, environment, health care, etc.</li> <li>• In smaller RCTs, outcomes can be biased by accidental inclusion of people who are much more or much less likely to respond to the intervention.</li> <li>• Effects are restricted to defined dose and intervention type.</li> <li>• RCTs usually have very strict inclusion and exclusion criteria, so the samples are often unrepresentative and results cannot be as widely generalized.</li> <li>• Attrition rate during the course of the RCT could bias the results.</li> <li>• Outcome reporting bias can influence results in which primary outcomes are changed, introduced or omitted since the original protocol.</li> <li>• Short time frame limits capacity to examine long-term interventions, which is particularly relevant for lifestyle changes that may lead to small, cumulative effects over years and decades such as cognitively stimulating activity.</li> </ul>

## 5. DISCLOSURE STATEMENT OF POTENTIAL FINANCIAL CONFLICTS OF INTEREST

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Each of the 27 GCBH experts participating in the formulation of this paper were asked to disclose potential conflicts of interest and provide other relevant disclosures. Twenty-one of the experts who participated in the meeting and contributed to the formulation of the recommendations attested they had no conflicts of interest. On the GCBH Governance committee, Dr. Ronald Petersen declared part-time consultation with several pharmaceutical companies. Among the issue experts selected to participate in this project, five experts provided the following financial disclosures related to their brain-health expertise. Dr. Tod Cooperman is president of ConsumerLab.com LLC, which operates a voluntary Quality Certification Program in which any supplement manufacturer can pay a fee to have a product tested for possible certification. Dr. Cooperman declared, “manufacturers have no influence on the certification process and ConsumerLab has no financial interest in the products or companies.” Dr. Steven DeKosky declared receiving consulting fees from several pharmaceutical companies including Amgen, Biogen and CognitionTherapeutics as well as receiving compensation for being an editor for dementia for the electronic textbook *Up-To-Date*. Dr. Francine Grodstein disclosed receiving unrestricted research grants from Nestle Waters Inc. and the California Walnut Commission. Dr. Timothy Kwok declared that he participated in an advisory board meeting organized by Merck on the use of nutritional supplement for brain health in January 2018. Dr. Gary Small disclosed that he has served as an advisor to and/or received lecture fees from AARP, Allergan, Avanir, Axovant, Forum Pharmaceuticals, Handok, Herbalife (a company that sells dietary supplements), Janssen, Lundbeck, Lilly, Novartis, Otsuka, Pfizer and Theravalues (a company that sells dietary supplements). Dr. Small also declared that he has a financial interest in TauMark LLC. These disclosures are available upon request by contacting staff of the Global Council on Brain Health. The authors are unaware of any affiliation that affected the objectivity of this paper and its recommendations.

## 6. FUNDING

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AARP provided the funding and staffing for the convening of the consensus meeting, conference calls and formulation of this consensus and recommendation paper. AARP paid for the travel costs associated with attending the in-person meeting and provided modest honoraria for the experts participating in the meeting Oct. 16-18, 2018, and for the participation of the experts in conference calls. Liaisons did not receive reimbursement or honoraria. Dr. DeKosky declined the honorarium.

## 7. SELECTED REFERENCES

- Agbabiaka, T. B., et al. (2018). "Prevalence of drug-herb and drug-supplement interactions in older adults: a cross-sectional survey." *Br J Gen Pract* 68(675): e711-e717. <https://doi.org/10.3399/bjgp18x699101>
- Authority), E. E. F. S. (2017). "Dietary reference values for nutrients: Summary report. EFSA supporting publication "EFSA supporting publication 2017 e15121: 92 pp. <https://doi.org/10.2903/sp.efsa.2017.e15121>
- Berti, V., et al. (2018). "Mediterranean diet and 3-year Alzheimer brain biomarker changes in middle-aged adults." *Neurology* 90(20): e1789-e1798. <https://doi.org/10.1212/wnl.0000000000005527>
- Blumberg, J. B., et al. (2018). "The Evolving Role of Multivitamin/Multimineral Supplement Use among Adults in the Age of Personalized Nutrition." *Nutrients* 10(2). <https://doi.org/10.3390/nu10020248>
- Chen, F., et al. (2019). "Association Among Dietary Supplement Use, Nutrient Intake, and Mortality Among U.S. Adults: A Cohort Study." *Ann Intern Med*. <https://doi.org/10.7326/m18-2478>
- Clifford, T., et al. (2018). "Effects of inorganic nitrate and nitrite consumption on cognitive function and cerebral blood flow: A systematic review and meta-analysis of randomized clinical trials." *Crit Rev Food Sci Nutr*: 1-11. <https://doi.org/10.1080/10408398.2018.1453779>
- Cyranoski, D. (2018). "Why Chinese medicine is heading for clinics around the world." *Nature* 561: 448-450. <https://doi.org/10.1038/d41586-018-06782-7>
- Dacks, P. A., et al. (2014). "Evidence needs to be translated, whether or not it is complete." *JAMA Neurol* 71(2): 137-138. <https://doi.org/10.1001/jamaneurol.2013.5376>
- DeKosky, S. T., et al. (2008). "Ginkgo biloba for prevention of dementia: a randomized controlled trial." *JAMA* 300(19): 2253-2262. <https://doi.org/10.1001/jama.2008.683>
- Dwyer, J. T., et al. (2018). "Dietary Supplements: Regulatory Challenges and Research Resources." *Nutrients* 10(1). <https://doi.org/10.3390/nu10010041>
- Fernandes, A. R., et al. (2006). "Dioxins and polychlorinated biphenyls (PCBs) in fish oil dietary supplements: occurrence and human exposure in the UK." *Food Addit Contam* 23(9): 939-947. <https://doi.org/10.1080/02652030600660827>
- Fibigr, J., et al. (2018). "Current trends in the analysis and quality control of food supplements based on plant extracts." *Anal Chim Acta* 1036: 1-15. <https://doi.org/10.1016/j.aca.2018.08.017>
- Gorelick, P. B., et al. (2017). "Defining Optimal Brain Health in Adults: A Presidential Advisory From the American Heart Association/American Stroke Association." *Stroke* 48(10): e284-e303. <https://doi.org/10.1161/str.000000000000148>
- Grodstein, F., et al. (2013). "A Randomized Trial of Long-term Multivitamin Supplementation and Cognitive Function in Men: The Physicians' Health Study II." *Ann Intern Med*. 159(806-814).
- Gupta, P. K., et al. (2001). "Processing liquid-based gynecologic specimens: comparison of the available techniques." *Acta Cytol* 45(6): 995-998. <https://doi.org/10.1159/000328377>
- Hellmuth, J., et al. (2019). "The Rise of Pseudomedicine for Dementia and Brain Health." *JAMA*. <https://doi.org/10.1001/jama.2018.21560>
- Heussner, A. H., et al. (2012). "Toxin content and cytotoxicity of algal dietary supplements." *Toxicol Appl Pharmacol* 265(2): 263-271. <https://doi.org/10.1016/j.taap.2012.10.005>
- Hunt, A., et al. (2014). "Vitamin B12 deficiency." *BMJ* 349: g5226. <https://doi.org/10.1136/bmj.g5226>
- Johnston, D. I., et al. (2016). "Hepatotoxicity associated with the dietary supplement OxyELITE Pro-Hawaii, 2013." *Drug Test Anal* 8(3-4): 319-327. <https://doi.org/10.1002/dta.1894>
- Kwok, T., et al. (2011). "A randomized placebo controlled trial of homocysteine lowering to reduce cognitive decline in older demented people." *Clin Nutr* 30(3): 297-302. <https://doi.org/10.1016/j.clnu.2010.12.004>
- Langan, R. C. and A. J. Goodbred (2017). "Vitamin B12 Deficiency: Recognition and Management." *Am Fam Physician* 96(6): 384-389.
- Littlejohns, T. J., et al. (2014). "Vitamin D and the risk of dementia and Alzheimer disease." *Neurology* 83(10): 920-928. <https://doi.org/10.1212/wnl.0000000000000755>
- Mengelberg, A., et al. (2018). "Fish oil supplement use in New Zealand: A cross-sectional survey." *Complement Ther Clin Pract* 33: 118-123. <https://doi.org/10.1016/j.ctcp.2018.09.005>
- Nourhashemi, F., et al. (2018). "Cross-sectional associations of plasma vitamin D with cerebral beta-amyloid in older adults at risk of dementia." *Alzheimers Res Ther* 10(1): 43. <https://doi.org/10.1186/s13195-018-0371-1>
- Parra, M. A., et al. (2018). "Dementia in Latin America: Assessing the present and envisioning the future." *Neurology* 90(5): 222-231. <https://doi.org/10.1212/wnl.0000000000004897>
- Patel, K. R. and A. Sobczynska-Malefora (2017). "The adverse effects of an excessive folic acid intake." *Eur J Clin Nutr* 71(2): 159-163. <https://doi.org/10.1038/ejcn.2016.194>
- Rawn, D. F., et al. (2009). "Persistent organic pollutants in fish oil supplements on the canadian market: polychlorinated dibenzo-p-dioxins, dibenzofurans, and polybrominated diphenyl ethers." *J Food Sci* 74(4): T31-36. <https://doi.org/10.1111/j.1750-3841.2009.01143.x>
- Rutjes, A. W., et al. (2018). "Vitamin and mineral supplementation for maintaining cognitive function in cognitively healthy people in mid and late life." *Cochrane Database Syst Rev* 12: CD011906. <https://doi.org/10.1002/14651858.cd011906.pub2>

Sattigere, V. D., et al. (2018). "Science-based regulatory approach for safe nutraceuticals." *J Sci Food Agric*. <https://doi.org/10.1002/jsfa.9381>

Scarmeas, N., et al. (2018). "Nutrition and prevention of cognitive impairment." *Lancet Neurol* 17(11): 1006-1015. [https://doi.org/10.1016/S1474-4422\(18\)30338-7](https://doi.org/10.1016/S1474-4422(18)30338-7)

Shade, M. Y., et al. (2018). "Analysis of oral dietary supplement use in rural older adults." *J Clin Nurs*. <https://doi.org/10.1111/jocn.14763>

Small, G. W., et al. (2018). "Memory and Brain Amyloid and Tau Effects of a Bioavailable Form of Curcumin in Non-Demented Adults: A Double-Blind, Placebo-Controlled 18-Month Trial." *Am J Geriatr Psychiatry* 26(3): 266-277. <https://doi.org/10.1016/j.jagp.2017.10.010>

Soininen, H., et al. (2017). "24-month intervention with a specific multinutrient in people with prodromal Alzheimer's disease (LipiDiDiet): a randomised, double-blind, controlled trial." *Lancet Neurol* 16(12): 965-975. [https://doi.org/10.1016/S1474-4422\(17\)30332-0](https://doi.org/10.1016/S1474-4422(17)30332-0)

Update, C. (1990). "Eosinophilia-myalgia syndrome associated with ingestion of L-tryptophan—United States, through August 24, 1990." *Morbidity and Mortality Weekly Report (MMWR)* 39: 587-589. <https://doi.org/10.1001/archderm.1990.01670340023001>

Vichi, S., et al. (2012). "Contamination by Microcystis and microcystins of blue-green algae food supplements (BGAS) on the Italian market and possible risk for the exposed population." *Food Chem Toxicol* 50(12): 4493-4499. <https://doi.org/10.1016/j.fct.2012.09.029>



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