

WITH A HEALTHY DIET.

EATING RIGHT IS IMPORTANT FOR HEART HEALTH AND BRAIN HEALTH!

Foods we eat are critical in maintaining our brain health. Learn how to eat smart below!



 Global Council on Brain-Food: GCBH Recommendations on Nourishing your Brain Health; GlobalCouncilonBrainHealth.org
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 Contact: GCBH@aarp.org + For more brain health tips see stayingsharp.org; DOI: https://doi.org/10.26419/pia.00019.002



Brain Food: GCBH Recommendations on Nourishing Your Brain Health



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 issue areas 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.

We know 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.

NUTRITION AND BRAIN HEALTH

On September 12 and 13, 2017, members of the GCBH met in Baltimore, Maryland to examine the impact of diet on brain health in adults age 50 and older. Throughout the discussion, experts examined the evidence on whether and how dietary patterns and food choices can influence brain health. The GCBH is planning a separate discussion and report addressing supplements, nutraceuticals and specific vitamins at a later meeting. For this report, the GCBH focused on the foods people eat. 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 for men and women age 50 and older. It also identifies gaps in our knowledge about diet 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 sizeable sample of the current evidence underpinning the GCBH consensus in this area.

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INTRODUCTION

These recommendations are based on the experts' evaluation of the best available evidence from observational studies and randomized controlled trials that link certain nutrients, food, and dietary patterns to better cognitive outcomes in older adults. The experts also considered a range of studies involving animal models that describe the mechanisms through which certain dietary patterns can improve or harm brain health. Research on the impact of the Mediterranean diet, DASH diet (Dietary Approaches to Stop Hypertension) and the MIND diet (Mediterranean-DASH Intervention for Neurodegenerative Delay) in particular have provided critical evidence on how diet can potentially affect brain health. Increasingly, research is showing that a healthy diet is crucial to optimal brain health.

The 2017 AARP Brain Health and Nutrition

survey found that people who often eat well-balanced and nutritious meals also reported better brain health.¹ Among individuals age 50 and older, three-quarters (75%) who said they ate well five to seven days per week reported their brain health/mental sharpness as "excellent" or "very good." Only about 40% of those who said they rarely or never ate well reported their brain health as high. See appendix 9, figure 1.

The experts agreed that foods and diets that are good for heart health are also good for brain health, lending support to the adage, "what's good for the heart is good for the brain." In support of this, some recent studies evaluating the incidence of dementia among large groups of people over several decades have found decreases in the age-adjusted incidence of dementia occurring simultaneously with improvement in cardiovascular health. The experts pointed to large, welldesigned epidemiological studies among populations in the United States, Great Britain, the Netherlands, Finland and Sweden corroborating this relationship. The 2017 AARP Brain Health and Nutrition survey also found that significantly more adults age 50 and over without heart disease rated their brain health/mental sharpness as "excellent" or "very good" compared to those with heart disease (64% vs. 50%).

Further details about the relationship between brain health and heart health and many other issues are provided in the discussion and knowledge gap section of this report. But we note that despite the promising decrease in age-adjusted incidence and/or delay of onset of dementia shown in these studies, the worldwide burden of dementia is still expected to increase as average life expectancy increases. This is particularly true for older adults, the economically vulnerable, and for those in low-to-middle income countries, as well as in countries where vascular risk factors continue to rise.

These GCBH recommendations are based on current peer-reviewed evidence suggesting that the recommended foods are beneficial to cognitive health. However, the data does not conclusively support that eating any of the recommended foods can prevent cognitive decline. More research in this area is recommended. Nonetheless, members of the GCBH feel confident in making the following consensus statements and recommendations.

¹ A nationally representative survey of individuals age 40 and older was conducted October 25-November 8, 2017. The final sample consisted of a total of 2,033 respondents. The margin of error for the full sample is ± 2.7 percentage points, the margin of error for subgroups is higher. All estimates in this document are for adults age 50 and older.

CONSENSUS STATEMENTS

These consensus statements and the recommendations that follow are based on extensive sources and research within nutritional science, basic science (with greater emphasis placed on human studies), well-designed randomized controlled trials and observational studies.² 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 sections and attached glossary at appendix 2.

- 1. Diet impacts brain health.
- **2.** What is good for the heart is good for the brain. Common conditions influenced by diet such as elevated blood pressure, high cholesterol, and diabetes harm both cardiovascular and cognitive health. Therefore, a heart healthy diet is a brain healthy diet.
- **3.** Long-term healthy eating habits promote good brain health.
- **4.** You can benefit from changing to a healthy diet at any age. However, the sooner you start the better.
- **5.** The typical, contemporary Western diet (high in salt, sugar, excess calories, and saturated fats) is not good for the brain. See a discussion of healthy diets including the Mediterranean diet, the DASH diet, the MIND diet and the Nordic diet below.
- **6.** No single food acts as a silver bullet for improving or maintaining brain health. The combination of different types of food and nutrients together in our diets likely determines health benefits.
- **7.** A plant-based diet that is rich in a variety of fruits and vegetables, particularly green-leafy vegetables and berries, is associated with better brain health.
- **8.** Consumption of fish, as well as other types of seafood, seems to benefit cognitive function. This may be due to the omega-3 fatty acid content.

- **9.** Multiple studies link high levels of saturated fat with cognitive decline. A diet that is higher in unsaturated fats and lower in saturated fats is linked to better cognition. See further discussion below.
- **10.** Excessive alcohol is bad for brain health.
- **11.** Excessive salt intake can contribute to high blood pressure. Because high blood pressure is an important risk factor for stroke, and strokes are detrimental to cognitive health, excessive salt intake is harmful for your brain health.

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 5.

EXPERT RECOMMENDATIONS

FOR INDIVIDUALS

A. ENCOURAGE:	B. INCLUDE:	C. LIMIT:
 Berries (not juice) Fresh vegetables (in particular leafy greens) Healthy fats (such as those found in oils, including extra virgin olive oil) Nuts (a high calorie food, so limit to a moderate amount) Fish and seafood 	 Beans and other legumes Fruits (in addition to berries, previously mentioned) Low fat dairy, such as yogurt Poultry Grains 	 Fried food Pastries Processed foods Red meat Red meat products Whole fat dairy, such as cheese and butter Salt

- We recommend the food guidelines in the table above for brain health. We encourage people to eat the "A-list" healthy foods regularly, include other "B-list" foods in their diet, but to limit the amount of "C-list" foods.
- **2.** If you don't drink alcohol, don't start drinking in order to protect your brain health. If you drink alcohol, do so in moderation, because it is unclear whether there is any beneficial level of consumption for brain health.
- **3.** Eat whole, non-processed foods to limit unintentional intake of too much salt, sugar, and saturated fats, which often appear in processed, packaged and fried foods.
- **4.** Be cautious when it comes to eating chocolate. Cocoa-rich products are generally high calorie because they often include sugar and high fat dairy products. Therefore, when incorporating chocolate in your diet, it is important to avoid excess weight gain, which could counterbalance, or even exceed, any benefits from eating cocoa.
- 5. Avoid trans fats.

FOR HEALTHCARE PROVIDERS

- **1.** Evaluating nutritional habits of patients should be part of good routine clinical care.
- **2.** Consider screening patients for nutrient deficiencies or excesses based on symptoms. Unless deficiencies are identified, we do not recommend routine supplementation.

PRACTICAL TIPS

- 1. Stay physically active to complement eating a healthy diet. Physical activity has been shown to improve cognition in adults and is important to promote healthy aging. Your diet should provide the nutrients and energy you need to maintain a good balance between energy intake from food and energy expenditure from physical activity. (See the <u>GCBH's Brain-Body Connection report</u> for a more thorough discussion on how physical activity helps brain health.)
- 2. Avoid eating in excess. Quantity and moderation of intake of nutrients matters. Too much of a good thing is often not good either. Using smaller plates is a very effective method for controlling portion sizes.
- 3. Eat at least one meal per week with fish that is not fried.
- **4. Look at the sodium content in prepared foods you are eating.** Baked goods, such as bread, canned soups and frozen foods are typically high in salt content that you may not realize you are eating. Note that frozen vegetables and fruit are typically low in salt and high in essential nutrients, while frozen, ready-to-eat meals are typically high in salt.
- **5. Use vinegar, lemon, aromatic herbs, and spices to increase flavor in food without increasing salt content.** Check the labels of spice blends to determine if they contain salt.
- 6. Consider dietary counseling if you are trying to overcome conditions such as hypertension, diabetes, and obesity.
- **7.** Snack on raw, plain, unsalted nuts; they may be beneficial for brain health. Nuts tend to be high-calorie foods because of high fat content, so they should be eaten in moderation.
- 8. Eat a wide variety of different colored vegetables. Try to add new vegetables to your diet and experiment with new ways of cooking and preparing vegetables.

- 9. Choose fresh, frozen or canned fruits and vegetables stored in water or their own juice. If you do buy canned vegetables or fruits with added salts or sugars, rinse them before eating. Look for vegetables without added salt, butter or cream.
- **10. Purchase food and prepare meals at home.** This gives you more control over the salt, sugar, and fat content than if you frequently buy prepared meals or food from restaurants.
- 11. Use mono and polyunsaturated fats in cooking. Usually these are the cooking oils that are in a liquid state at room temperature. Avoid manufactured oils with partially hydrogenated fats and animal fats such as lard and butter. Unsaturated fats seem to be beneficial to heart health and are also thought to be beneficial to brain health. Unsaturated fats are often found in liquid oils such as olive oil, canola oil (also known as rapeseed oil), corn, and safflower oils, as well as walnuts and certain fish.
- **12. Read packaged food labels to help you choose healthier options.** The nutrition facts panel and ingredients list provides helpful information, such as saturated fat, sodium and sugar content.

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 nutrition. These experts have conducted research that significantly contributed to the body of evidence that links diets with brain health in older adults. Their diverse areas of expertise represent perspectives from disciplines including nutritional epidemiology, geriatric psychiatry, human nutrition science, gastroenterology, genomics, gerontology, internal medicine, neuropsychology, neurology, neuroscience, physiology, and public health.

Eleven issue specialists from four continents were asked to critically examine the state of the science as of September 2017. They discussed findings from observational 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 individuals to maintain and improve brain health. The issue specialists considered 13 different questions as a framework to guide their deliberations. The complete list is available in appendix 3.

After an in-depth moderated discussion, several followup conference calls and an exchange and refinement of drafts, the issue specialists arrived at 11 consensus statements to summarize the impact of diet on brain health. Based on their consensus, they made numerous recommendations related to nutrition in the context of brain health and cognitive decline. Further, they agreed on 12 practical tips to help people around the world adopt behaviors to improve their brain health.

Liaisons from civic and non-profit organizations with relevant expertise in brain health were invited to provide input and technical feedback during the refinement of the draft recommendations.

Two Governance Committee members attended the meeting in Baltimore. The entire Governance Committee reviewed and finalized the document during subsequent conference calls and emails with the issue experts between October 2017 and December 2017. 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. The GCBH Governance Committee reviewed this summary document to decide whether it accurately reflected the expert opinions expressed and the current state of science in the field. The Governance Committee approved the document on December 20, 2017.

DISCUSSION

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 nutrition and brain health. People make choices every day about what to eat. Waiting until definitive evidence exists on all the issues related to food 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.

These recommendations are meant for all healthy adults, particularly focusing on men and women age 50 and older who have not been diagnosed with a neurodegenerative disease such as Alzheimer's disease. The intent is to be as inclusive as possible for people as they age.

CONTEXTUAL FACTORS MATTER IN TAILORING RECOMMENDATIONS TO ANY PARTICULAR INDIVIDUAL

Making wise choices about your diet is something you can do to promote better brain health and choosing healthier options more often can have long term benefits. Nutritional value, type of food, quantity and quality, setting, convenience, and cost all factor into the complex choices you need to make when you choose one food over another. But each of these individual choices is made within a broader context that helps to shape a person's daily diet over his or her lifespan.

Nutritional recommendations need to be tailored to take into account your state of health, lifestyle and culture. It is always wise to consult with a health care provider before beginning or significantly changing your diet, particularly if you are currently managing health conditions or taking medications. A person's environment and what is practically and economically feasible must also be factored into plans to sustain healthy food choices.

Most, if not all cultures, place a high degree of importance on food. Food is a cornerstone of cultural and religious practices and celebrations around the world. People place great importance on the flavor, smell and presentation of food, and food choices are often made as part of cultural traditions. We know that the cultural traditions of family and friends can powerfully influence the food choices people make every day.

DIETARY PATTERNS

No single food is key to good brain health, but rather a combination of healthy foods is likely to help protect the brain. See appendices 4a and 4b. The pattern of your whole diet over your life span affects your brain health. There is growing evidence that micronutrients (such as vitamins and minerals) offer the greatest benefit when consumed as part of a balanced diet. While scientists continue to investigate the contributions of individual micronutrients to overall dietary patterns, research over the past several decades has highlighted the importance of eating patterns and maintaining a balance between food groups. Members of the GCBH provided examples of different brainhealthy diets during our discussion that have garnered headlines in recent years.

The Mediterranean diet, common in countries such as Greece, Italy and Spain, has received widespread media attention. It is characterized by high intake of monounsaturated fat (with extra virgin olive oil as the main source), vegetables, fruits, plant proteins, whole grains and fish. The Mediterranean diet also typically includes low consumption of red meat, refined grains and sweets. Moderate intake of wine accompanies this diet. Among other health benefits, studies have shown that this diet can lower risk of cardiovascular disease and can help manage diabetes. *The Nordic diet* draws upon many locally sourced foods traditionally consumed in Scandinavian countries including Denmark, Finland, Iceland, Norway, and Sweden. Similar to the Mediterranean diet, there is an emphasis on plant-based foods, such as fruits and vegetables, as well as meat, fish and oils. Key differences between the Mediterranean diet and Nordic diet include differences in types of individual fruits, vegetables and cereal used, differences in cooking methods, and differences in the type and quantity of oil that is used. The Nordic diet uses rapeseed oil, also known as canola oil, instead of olive oil.

The DASH (Dietary Approaches to Stop Hypertension)

diet: emphasizes low sodium and portion size and is associated with health improvements in blood pressure, blood lipids and other benefits linked to reduced risk of chronic disease. The DASH diet is a plant-focused diet, rich in fruits, vegetables and nuts, with low-fat and nonfat dairy, lean meats, fish, and poultry, mostly whole grains, and heart healthy fats.

The Okinawan diet: This diet is based on the eating habits of the indigenous people of the Ryukyu Islands in Japan, who are recognized as having exceptional longevity. The diet emphasizes yellow, orange and green vegetables; includes soy and legumes and low amounts of meat, refined grains, sugar, salt or dairy. The diet features large percentage of sweet potatoes (purple yams), and the Okinawans tend to eat less rice and fish than their other Japanese counterparts. They also eat until they are 80% full in order not to overeat, a practice called *hara hachi bu*.

The MIND (Mediterranean – DASH Intervention for Neurodegenerative Delay) diet: The MIND diet draws from both the Mediterranean and the DASH diets and includes an abundance of vegetables, whole grains and a daily glass of wine. It recommends green leafy vegetables six times a week, other vegetables at least once a day and two or more servings a week of berries. It also advocates snacking on nuts most days, eating beans every other day, poultry twice a week and fish at least once a week. Dieters should limit eating unhealthy foods, such as butter, cheese, and fried or fast food. It highlights blueberries and leafy greens as especially beneficial for the brain.

MAKING CHANGES TO YOUR DIET

It is never too late to start eating a healthy diet, such as those suggested above. Improvements in your diet can help your brain health and lower your risks of cognitive decline whenever you decide to start. Making small practical changes, such as those recommended here by the GCBH, is a useful and sustainable way to maintain a healthier diet. These can then be built upon by incorporating additional changes to build a brain healthy lifelong dietary pattern.

A September 2017 article published in JAMA (Journal of the American Medical Association) points out that "changing lifelong nutrition behaviors can seem overwhelming, but even exceedingly small shifts can have an effect."3 For example, "increasing fruit intake by just 1 serving per day has the estimated potential to reduce cardiovascular mortality risk by 8%, the equivalent of 60,000 fewer deaths annually in the United States and 1.6 million deaths globally. Other examples include reducing intake of sugar-sweetened beverages, fast food meals, processed meats, and sweets, while increasing vegetables, legumes, nuts, and whole grains." When you replace potato chips and sour cream dip with nuts or carrots and hummus, for example, you lower trans fats and saturated fats and increase whole grain and vegetable intake, while still having a satisfying snack.

Practical tools and tips for adopting healthy eating habits, specifically targeted to issues relevant to the age 50 and over population, can be found in **MyPlate for Older Adults**. See appendix 4a. This resource encourages consumption of colorful food choices, healthy oils, and a variety of whole grains and proteins. Nutrition scientists at Tufts University partnered with the **AARP Foundation** in 2015 to revamp *MyPlate for Older Adults* following the updated **2015-2020 Dietary Guidelines for Americans**.

Another good source of information for people trying to improve their diet and exercise habits is the guide to **Changing Your Habits for Better Health**, from the National Institutes of Health. See the further discussion below about behavior change in the knowledge gaps section.

³ http://jamanetwork.com/journals/jama/fullarticle/2653762

Simply incorporating more fruits and vegetables into your diet appears to be helpful. According to the 2017 AARP Brain Health and Nutrition survey, adults age 50 and older who get the recommended amount of fruits and vegetables in a typical day report significantly better brain health compared to those who do not get the recommended amount (70% vs. 61%). The survey found that the more fruits and vegetables men and women consume, the more likely they are to rate their brain health higher. Of those who said they don't eat any vegetables, fewer than half (49%) considered their brain health as "excellent" or "very good." See appendix 9, figure 2.

BRAIN HEALTH AND ALCOHOL CONSUMPTION

There is a lot of interest about whether alcohol is good or bad for brain health. The Mediterranean and MIND diets typically include a moderate amount of wine, and studies showing the benefits of wine have generated many headlines. The Mediterranean diet includes wine consumed with meals, and generally no more than 5 ounces (148 milliliters) of wine daily for women, and no more than 10 ounces (296 milliliters) of wine daily for men. The benefit of red wine on brain health reported in studies on the Mediterranean diet may be related to components in the wine such as polyphenols (micronutrients found in plant-based foods). These micronutrients may act as antioxidants which affect blood pressure, and which are not typically contained in spirits or beer.

The Dietary Guidelines for Americans notes the short and long term risks with alcohol consumption and recommends that if any alcohol is consumed, it should be done only in moderation, meaning up to one drink per day for women and two drinks per day for men. The Dietary Guidelines for Americans defines a standard drink as containing 0.6 ounces (14.0 grams or 1.2 tablespoons) of pure alcohol. Generally, this amount of pure alcohol is found in 12-ounces of beer (5% alcohol content), 8-ounces of malt liquor (7% alcohol content), 5-ounces of wine (12% alcohol content), 1.5-ounces of 80-proof distilled spirits or liquor such as gin, rum, vodka or whiskey (40% alcohol content). As you age, your body processes alcohol differently, and experts often recommend older people consume even smaller quantities.

Neither the GCBH nor the Dietary Guidelines for *Americans* recommends that anyone begin drinking alcohol if they do not already do so. While there is some evidence that moderate alcohol consumption can have protective health and cognitive benefits, recent studies indicate there are also adverse effects on the brain from alcohol consumption. Alcohol consumed even in moderate quantities has been associated with adverse brain health outcomes. There are both shortterm and long-term risks associated with excessive alcohol consumption, including learning and memory problems. In the United Kingdom, for example, drinking guidelines from 1987 were updated in 2016 to reflect new research findings and lowered the amount of alcohol consumption considered to be safe. The updated United Kingdom 2016 guidelines call for no more than 14 drinks over the course of a week for men or women, which is still significantly more than the United States' recommendations.

Moreover, in some groups of people the consumption of any kind of alcohol, including red wine, is discouraged. Women at a higher risk for breast cancer, for example, should consider limiting alcohol because studies have found that even moderate alcohol use increases breast cancer risk. Individuals below age 21 are strongly advised not to drink alcohol.

HARMFUL DIETARY FATS / HEALTHIER DIETARY FATS

The primary dietary sources for trans fats in processed food are "partially hydrogenated oils." Look for them on the ingredient list on food packages. Trans fats raise your harmful (LDL) cholesterol levels and lower good (HDL) cholesterol levels. Eating trans fats increases risk of developing heart disease, stroke and type 2 diabetes. All of these diseases can harm the brain and increase risk of cognitive decline. Trans fats are found in processed foods, fried foods like doughnuts, and baked goods including cakes, piecrusts, biscuits, frozen pizza, cookies, crackers, margarines and other spreads, though many companies have made great strides in eliminating trans fats from these products. Healthier dietary fats include monounsaturated fatty acids and polyunsaturated fatty acids, particularly omega-3 fatty acids. For a full description of different types of dietary fats, see appendix and recommendations.

Regulations surrounding trans fats is an evolving area of health policy around the world. In many countries, vegetable oils with trans fats are found everywhere—in pastries, bakeries, supermarkets, etc... In the United States, the Food and Drug Administration has set 2018 as the deadline to rid foods of trans fats. This announcement was made in 2015 when the FDA gave the food industry three years to eliminate trans fats from the food supply. At the time of this review, four member states of the European Union (EU) have set legal limits on industrially produced trans fats in foods (Denmark, Austria, Hungary, Latvia). There has been growing pressure to establish this as an EU-wide practice. In a report on trans fats published in December 2015, the European Commission concluded that a legal limit for industrial trans fat content would be the most effective measure for tackling the problem. The European Union is currently working on legislation that would regulate and reduce trans fat content in foods.

FISH, OMEGA-3 FATTY ACIDS AND BRAIN HEALTH

The present document only refers to the evidence on food sources of omega-3 polyunsaturated fatty acids and not on supplements. The impact of omega-3 fatty acids on the brain has been extensively studied, and there is an abundance of information on the link between omega-3 fatty acids and healthy brain aging. Studies examining the role of omega-3 fatty acids have widely considered omega-3 fatty acids together as a whole rather than looking at the specific types of omega 3 fatty acids: EPA, ALA and DHA. DHA is the most prevalent omega-3 fatty acids in the brain and has been shown to play an important role in the maintenance of neuronal membranes.

There is growing recognition of the importance of incorporating omega-3 fatty acids into diet. Fish is a good source of protein and omega-3 fatty acids, and it constitutes an important part of the Mediterranean, Nordic, DASH, Okinawan and MIND diets as described earlier. Those who typically eat fish or other seafood every week report better brain health compared to those who never ate fish or seafood, according to the 2017 AARP Brain Health and Nutrition survey. In fact, 67% of those who eat fish or seafood reported their brain health as "excellent" or "very good." See appendix 9, figure 3.

Fish is also easily accessible to consumers in many regions of the world. Communities near the Pacific Ocean, for example, have easy access to fish. In some areas, fish is even cheaper than meat. In some regions of the world, such as Asia, however, there is concern about the mercury content in some fish, which may have adverse health effects since the heavy metal cannot be eliminated. This is a topic of ongoing investigation, and the impact may depend on the level of mercury consumed through contaminated fish. In the additional resources section, we reference the Monterey Seafood websites that provide information on mercury levels in fish caught in the United States and Canada.

It should also be noted that omega-3 fatty acids are found in sources other than fish. Plant sources of omega-3 fatty acids include flaxseed, oils (olive, canola, flaxseed, soybean), nuts and other seeds (walnuts, butternut squash and sunflower). Replacements for vegans/ vegetarians exist that are not supplements, but the evidence is not as robust for plant sources of omega-3 fatty acids.

SALT AND APPROACHES TO QUANTITY

There is a well-established relationship between consuming high levels of sodium and risk of stroke. In Japan, a public health education intervention in the 1960s showed the effectiveness of dietary interventions to reduce sodium intake. A 50% reduction in salt in the diet was associated with an 85% reduction in mortality caused by stroke.

Current recommendations from the Dietary Guidelines for Americans are to limit sodium intake to 2,300 mg/ day, which amounts to about one teaspoon of salt. The American Heart Association recommends an ideal limit of 1,500 mg/day.

SALT VS. SODIUM EQUIVALENTS

Sodium chloride or table salt is approximately 40 percent sodium. It's important to understand just how much sodium is in salt so you can take measures to control your intake. These amounts are approximate.

> $\frac{1}{4}$ teaspoon salt = 575 mg sodium $\frac{1}{2}$ teaspoon salt = 1,150 mg sodium $\frac{3}{4}$ teaspoon salt = 1,725 mg sodium 1 teaspoon salt = 2,300 mg sodium

The majority of salt in most people's diets comes through processed foods and baked goods rather than added table salt. An estimated half of the sodium in the Western diet comes from eating bread and other baked goods. Although we are unaware of studies that definitively tie high sodium intake to poor cognitive health, we feel confident saying that reducing high levels of salt is likely to have a positive benefit on brain health through its effects on blood pressure.

COFFEE/CAFFEINE/TEA

Several studies have found an association between drinking coffee and tea and decreased risk of cognitive decline and dementia. There is plausible reason to believe that compounds in tea and coffee called polyphenols may have antioxidant benefit. However, there is no consensus on whether, and at what amounts, tea and/or coffee may be beneficial or harmful for brain health. Short-term effects of caffeine consumption from coffee and tea have been shown to increase alertness and cognitive performance, but the long-term effects are less understood. There have been several studies suggesting that those who drink coffee have better cognitive function over time than those who drink less coffee. However, it is possible that the caffeine or compounds in coffee and tea may not be the cause of improved outcomes, but rather that people who drink tea and coffee are also more likely to have higher education levels or better health, which are tied to improved cognitive performance and lower risk of dementia. While we are not aware of moderate tea or coffee consumption causing harm to cognitive health, if you don't currently drink coffee and tea with caffeine, we don't recommend that you start to do so for your brain health.

COCOA FLAVONOIDS

In recent years, a growing body of evidence suggests that cocoa flavanols often found in dark chocolate can improve cognitive function, though the extent to which they can do so is an ongoing topic of research. Compounds widely present in plant-based foods, called flavonoids, may be associated with a lower risk of cognitive impairment and better cognitive function. Flavanols are a type of polyphenol, a chemical compound found in plant-based foods. A sub-class of flavonoids is found in cocoa, chocolate and a variety of fruits and vegetables, such as grapes, red wine, apples, tea and cocoa products. A limited number of experimental trials, primarily funded by industry, have demonstrated that short-term consumption of special preparations of cocoa flavanols boost cognitive performance. Nevertheless, clear-cut associations with cocoa flavanols and decreased risk for dementia and Alzheimer's disease have not been established.

GRAINS

There have been several well-done studies on the relationship of whole grains to conditions such as diabetes and coronary heart disease, suggesting benefit for increased consumption of whole grains. People in Scandinavian countries tend to consume whole grains in much higher quantities. Whole grains are rich in fiber and B vitamins, as well as vitamin E and some trace minerals, including iron, magnesium and zinc. However, while whole grains have been a topic of much research, we are unaware of a study examining the benefit or detriment of whole grains as compared to refined grains on brain health. While the typical Japanese diet contains high consumption of refined white rice, the Japanese population appears to have relatively good cognitive health. Therefore, currently there is insufficient evidence to make a recommendation in this area.

PROCESSED FOODS

There is considerable debate over the definition of "processed" foods, which technically means "any food that has been altered in some way during preparation." The typical pejorative use implies any industrial food that has added fats, sugars and salt designed to improve taste and encourage consumption of the product. Such foods often have a low ratio of essential nutrients to harmful components (e.g. energy, added sodium and sugar). However, this ratio can be manipulated by adding vitamins, minerals, food dye, and artificial sweeteners to highly processed food. The regulation of processed foods and food additives varies widely between countries. Public perception surrounding some additives, such as high fructose corn syrup used to sweeten many candies and sodas, has been so negative in places such as the United States that there was an unsuccessful petition a few years ago to change the name from corn syrup to "corn sugar."

Grains that are <u>not</u> hyper-enriched should be included in your diet. Some breakfast cereals are highly enriched with vitamins and minerals. There are several studies that suggest that a few of the vitamins and minerals in these products, considered supplements at these levels, are associated with higher all-cause mortality. This is one of the challenges posed by processed foods, but we do not have sufficient evidence to make a particular recommendation in this area. Some researchers have taken a food systems approach. This means taking a broad view of how food affects the wider world and the lives of the people who grow, manufacture, and consume it. Studies have explored whether a higher proportion of industrialized food relates to the prevalence of chronic diseases in certain populations. However, as in the present document, there is considerable debate in how to use and precisely define the currently vague definition of processed foods. Some argue that the difficulty of defining whether processed foods contribute to negative health outcomes focuses too much on the processing itself rather than the nutrient density of the food.

COOKING AND QUALITY OF DIET

Research has found that frequently cooking at home results in better diet quality and improved health and weight in adults. Cooking methods can affect nutritional benefit of foods. For example, there are benefits of low temperature cooking as compared to high temperature cooking such as grilling or frying. Cooking methods such as barbecuing, frying and grilling can generate harmful chemical compounds that may promote inflammation and harm brain health. Although there is no conclusive evidence to date, it may be prudent, when possible to replace high-temperature cooking methods with boiling, poaching, steaming, or baking.

GLUTEN-FREE DIET

In recent years there has been growing interest in how a gluten-free diet might affect brain health. Gluten is the main protein component of wheat, rye, and barley. Common foods containing gluten include breads and pastas, cookies, muffins, and breakfast cereals. A gluten-free diet is the only proven treatment for celiac disease, an immune-based disease affecting nearly 1% of the United States population. In people with celiac disease, dietary gluten triggers an immune reaction that results in intestinal damage. The symptoms of celiac disease include intestinal symptoms such as abdominal pain and diarrhea, but can also include non-intestinal symptoms including headache, osteoporosis, and fatigue. Anecdotally, many patients with celiac disease report that when they are unintentionally exposed to gluten they develop recurrent symptoms that often include transient cognitive problems, including word finding and memory difficulties. This phenomenon, often referred to as "brain fog," is not well understood, and the mechanism by which gluten triggers these

cognitive symptoms is unknown. One small study of 11 people newly diagnosed with celiac disease found that verbal fluency scores improved one year after starting a gluten-free diet.

Most studies show that that the majority of individuals in the United States with celiac disease have not been diagnosed, though undiagnosed celiac disease is unlikely to be a common cause of cognitive impairment, since celiac disease is present in less than 1% of the population. In addition to those with celiac disease, there are also people who describe symptoms including "brain fog" that improve on a gluten-free diet, and yet do not have celiac disease. These people are said to have non-celiac gluten sensitivity. Because there is no test to diagnose this condition, this diagnosis is usually made after a test for celiac disease produces a negative result. Despite popular claims that gluten contributes to cognitive problems in the general population, there is no evidence to suggest that gluten has an effect on mental function in people without celiac disease or nonceliac gluten sensitivity. Given the principle that "what is good for the heart is good for the brain," it is relevant to note that diets high in gluten have not been linked to heart attack risk. In fact, a low-gluten diet, if it is low in beneficial whole grains, could pose an increased risk of coronary heart disease.

RELATIONSHIP TO OTHER CHRONIC DISEASES

Many adults aged 50 and older have more than one chronic health condition such as heart disease or diabetes that are affected by diet. There are similarities between the diet recommended here for reducing risks for cognitive decline as a person ages and diets that are often recommended for several other chronic health problems. For example, the Mediterranean and DASH diets described above have been recommended by the American Diabetes Association for the management of diabetes and the DASH diet was developed to treat or prevent high blood pressure. Large, long-running clinical trials have established that the Mediterranean diet protects from heart disease and stroke, and as we have said earlier, heart health and brain health are intricately tied together. It is always a good idea to consult your health care provider about changes in your diet, particularly if you taking medications for chronic conditions.

WEIGHT LOSS

Many people are interested in the relationship between weight and cognitive health. A number of studies have linked obesity in midlife with an increased risk for future cognitive decline, and some studies suggest that a reduction in obesity could contribute to preventing or delaying dementia. Other studies have cautioned, however, that lowering weight may not be protective in older age. If you want to lose weight, one effective method is controlling portion sizes by using smaller plates. And if you want to optimize your diet for brain and heart health at the same time, another method is to eat lower calorie nutritious foods with unsaturated fats instead of foods with higher calories and saturated fats. For example, instead of putting butter on bread, try dipping the bread in extra virgin olive oil, or sprinkle a few nuts instead of cheese on your salad. The key, however, is to have moderate intake of food and calories. As the practical tips point out, the ideal diet should provide the nutrients and energy you need to maintain a good balance between energy intake from food and energy expenditure from physical activity, so that you maintain a healthy weight throughout your lifespan.

KNOWLEDGE GAPS: WHERE MORE RESEARCH IS NEEDED

In addition to the areas mentioned in the discussion section above, there are many other areas where more research is needed to better understand the impact of nutrition on brain health in adults.

THE RELATIONSHIP BETWEEN HEART HEALTH, DEMENTIA AND DIET

The FINGER study (The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability) a two-year, randomized, controlled trial of 1,260 Finnish men and women, found that a combination of healthy lifestyle factors, including diet, may be crucial to preventing dementia and maintaining memory and thinking skills. Researchers found a group that participated in a program that included exercise, nutritional counseling, computer-based brain training, social activity, and management of heart health risk factors had improved scores on cognitive tests and a decreased risk of cognitive decline, compared to the control group. Nutritionists counseled participants to follow the Finnish nutritional recommendations that includes include fruits and vegetables, whole-grain cereals, low-fat milk, margarine and rapeseed oil (similar to canola oil) and fish at least twice a week.

As noted in the introduction, there have been several large studies in Western Europe and the United States suggesting that there is a relationship between decreasing prevalence of dementia and improved heart health. This lends support to the notion that diets that can lower your risk for cardiovascular disease might also lower your risk for neurodegenerative disorders such as dementia. For example, results from the Framingham Heart Study in Massachusetts in the United States, show that participants studied over a 30 year period experienced a decline in the age-specific incidence of dementia at the same time that they showed decreases in their cardiovascular risk factors and improvements in many indicators of their cardiovascular health.

These studies are encouraging in that they have identified a trend over time showing that there may be ways to reduce risk for dementia or delay its onset. But these studies do not establish cause and effect, nor are they meant to be conclusive. The many possible factors responsible for this trend must be studied more extensively to better understand what contributed to the decline.

This report does not suggest that eating a heart-healthy diet will prevent dementia. While we do not yet know what causes dementia, there are many contributing risk factors leading to the development of the disease, and managing your diet to lower cardiovascular risk factors is only one part of the equation. Unfortunately, having good heart health will not guarantee good brain health. Despite knowing the strong relationship existing between a healthy heart and a healthy brain, we know it's not a one-to-one relationship. So while the GCBH is confident a heart healthy diet is also good for brain health, the relationship between diet and prevention of cognitive decline and dementia needs further research.

EFFECTIVE APPROACHES TO PROMOTE ADOPTION OF HEALTHY DIETS

Many barriers exist to practicing healthy dietary behaviors. Consumers face a deluge of advertisements every day promoting unhealthy foods that tend to be inexpensive and have large portions.

To counter these barriers, researchers recommend that behavioral improvements be approached incrementally and with the support of others. Nutritional counseling and input from healthcare providers are a few ways to increase awareness among patients of the positive steps they can take to change their diet. A report released in 2017 by the Office of Disease Prevention and Health Promotion in the United States estimated that only 12% of healthcare related office visits included counseling about diet, leaving much room for progress in this area. Nutritional interventions designed to integrate clinical care and community resources can make a big impact. There is great need for research into the most effective approaches to promote the adoption of a well-balanced diet and better lifestyle choices. More work in this area will help health care professionals, public health officials, and policy makers better understand how to influence the quality of our food system as a whole and habits at an individual level.

There are significant knowledge gaps around how to best work together to encourage better lifestyle choices and habits of individuals, including how to encourage better diets. Most evidence around effective dietary interventions comes from relatively short-term trials. As the World Health Organization has pointed out, there is scant scientific literature on the longterm effects, sustainability, and cost-effectiveness of changing dietary patterns in public health and there is "still a lack of information on interventions in low- and middle-income countries, and thus an urgent need for further research in these settings, and for scaling up the monitoring and evaluation of interventions."

NUTRITIONAL NEEDS DIFFER ACROSS THE LIFESPAN

Nutritional needs vary across the lifespan. Just as nutritional needs during childhood are distinct, so too are the needs of people in later life. As people age, nutritional deficiencies pose a challenge as difficulties absorbing nutrients becomes more common. Deficiencies in some micronutrients, such as vitamin B12, have been linked cognitive dysfunction in older adults. In cases of individuals with Alzheimer's disease, studies have highlighted lower plasma levels of Vitamin A, B12, C, E, folate and other nutrients. In individuals who may be struggling to maintain normal serum vitamin B12 levels, healthcare professionals must tailor nutritional advice given to those patients. For example, advice to limit red meat may be widely given to other patients, but consumption may actually be encouraged in patients with B12 and iron deficiency if the healthcare provider deems this to be appropriate.

These considerations underscore the many decisions that together make up an individual's diet. Additional research is needed to better understand the tradeoffs that exist when swapping different types of foods in place of others. For example, clinical trials have been conducted that showed a reduction in the incidence of cardiovascular disease when replacing saturated fats with polyunsaturated fats. Yet, by contrast, other studies reported no reduction in cardiovascular disease when carbohydrates replace saturated fats. There have not been any large, definitive studies researching the potential health benefits of substituting saturated fats with healthy carbohydrates as part of a lower fat, higher fruit, vegetable and grain diet.

The GCBH plans to focus on individual micronutrients and supplementation in an upcoming report. More research on the effect of diet over the course of a lifetime needs to take into account different nutritional needs as people age.

HYDRATION AND WATER

As people age, their ability to perceive thirst diminishes. Dehydration is common in older people due in part to these reduced thirst mechanisms, and dehydration is a leading cause for admission to emergency rooms and hospitals for older individuals. The link between hydration status and cognitive ability and mood is increasingly being recognized. Dehydration often leads to cognitive problems in older people, which can be assessed by examining changes in short-term memory, numerical ability, psychomotor function, and sustained attention. Researchers have found that even moderate dehydration is associated with confusion, disorientation and cognitive deficits. The degree to which thinking skills are affected is dependent on the severity of dehydration. The extent to which observed cognitive performance and associated neural activity is reversible with rehydration is a topic of ongoing investigation. Additional water intervention studies are therefore needed to understand how hydration status may affect cognitive health in the long-term, particularly in vulnerable populations prone to dehydration (e.g. nursing home residents). Research in this area can lead to new intervention programs and may have widespread public health implications.

CONCLUSION

With the diversity in cultural practices and lifestyle habits around the world, there are many ways to approach dietary choices. There is no one formula to healthy living, but prioritizing a well-balanced diet will put you on a path to optimizing both your overall health and brain health.

As further developments occur in the study of the impact of nutrition on brain health, the GCBH will periodically revisit these recommendations and provide updates when appropriate.

APPENDICES

- 1. PARTICIPANTS, WITH PARTICIPANTS' AND LIAISONS' LIST OF ADDITIONAL RESOURCES
- 2. GLOSSARY
- 3. DISCUSSION QUESTIONS FRAMING THE DELIBERATIONS
- 4a. MyPLATE DIETARY RECOMMENDATIONS
- 4b. SELECT DIETARY RECOMMENDATIONS FROM GOVERNMENTS REPRESENTED BY GCBH ISSUE EXPERTS ACROSS THE GLOBE
 - 5. DIFFERENCES, STRENGTHS AND LIMITATIONS OF TWO STUDY TYPES IN HUMANS
 - 6. DISCLOSURE STATEMENT OF POTENTIAL CONFLICTS OF INTEREST
 - 7. FUNDING
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 - 9. FIGURES

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PARTICIPANTS AND LIAISONS' LIST OF ADDITIONAL RESOURCES

- The American Heart Association. See: http://www.heart.org/brainhealth
- The Brain Health Resource from the Administration on Community Living (ACL).
 See: <u>https://www.acl.gov/node/293</u>
- Center for Disease Control and Prevention (CDC) website on:

Added sodium (salt). See: <u>https://www.cdc.gov/</u> salt/pdfs/sodium_role_processed.pdf

Sugars. See: https://www.cdc.gov/nutrition/ data-statistics/know-your-limit-for-addedsugars.html

- Dietary Guidelines. See: <u>https://health.gov/</u> <u>dietaryguidelines/2015/guidelines/</u>
- Monterey Bay Aquarium's Seafood Watch. See:

http://www.seafoodwatch.org/consumers/ seafood-and-your-health

http://www.seafoodwatch.org/resources/ seafood-and-human-health-resources

Resources from the National Institutes of Health (NIH):

National Institute on Aging (NIA) Go4Life Resource. See: https://go4life.nia.nih.gov/

National Institute on Aging (NIA) Healthy Eating Resource. See: <u>https://www.nia.nih.gov/health/</u> healthy-eating National Institute of Health (NIH) – What's A Standard Drink? See: <u>https://www.</u> <u>rethinkingdrinking.niaaa.nih.gov/How-muchis-too-much/What-counts-as-a-drink/Whats-A-Standard-Drink.aspx</u> United Kingdom National Health Service (NHS) website on eating processed foods. See: https://www.nhs.uk/Livewell/Goodfood/ Pages/what-are-processed-foods.aspx

2. GLOSSARY

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

BRAIN HEALTH

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

COGNITIVE DECLINE

The Institutes 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.

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 daily functioning. Though dementia generally involves memory loss, memory loss has different causes. So memory loss alone doesn't mean you have dementia. Alzheimer's disease is the most common cause of a progressive dementia in older adults, but there are a number of causes of dementia. Depending on the cause, some dementia symptoms can be reversed.

DIET

A specific, habitual pattern of food, drink, and nutrient choices. Some diets are tied to health goals, such as cognitive health, weight-loss, or heart health, but diets can also reflect a regional culture.

DIETARY FATS

One of the six nutrient groups utilized by the body.

UNSATURATED FATS

Unsaturated fats, have one or more double bond in the fatty acid chain. Polyunsaturated fats have more than one carbon bond in the molecule, while monosaturated fats have one carbon bond in the molecule. Vegetable oils, such as olive oil, contain unsaturated fats. They are typically liquid at room temperature.

SATURATED FATS

A group of fats that have no double bonds between carbon molecules because they are "saturated" with hydrogen molecules; often found in animal byproducts, such as red meat and whole dairy products. They are usually solid at room temperature.

TRANS FATS

Naturally occurring trans fats are found in small amounts in meat and dairy products. Artificial trans fats are formed during the hydrogenation of vegetable oils into solids. Often called "partially hydrogenated oils" on food packages. They are found in doughnuts, cookies, pastries and vegetable shortening.

EPIDEMIOLOGICAL STUDIES

(which can be cross-sectional or longitudinal). 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).

INTERVENTION

Any measure whose purpose is to improve health or alter the course of disease.

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.

NUTRIENTS

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.

PROCESSED FOODS

Food processing is any deliberate change in a food that occurs before it's available for us to eat. The International Agency for Research on Cancer (IARC) classified processed meat as "meat that has been transformed through salting, curing, fermentation, smoking or other processes to enhance flavor or improve preservation."

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 trial, 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 (due to Alzheimer's disease or another related disorder) is one condition, and cognitive decline (the slowing of thinking and memory 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 injuries among people who are involved in automobile accidents, but we nevertheless now recommend people wear seatbelts while they are driving.

WHOLE FOODS

Foods that are as close to their natural form as possible and are free from additives or other artificial substances.

3. DISCUSSION QUESTIONS FRAMING THE DELIBERATIONS

The GCBH did not address supplements, nutraceuticals or specific vitamins at this meeting.

- 1. Does diet impact brain health?
- **2.** What is the best evidence that a diet rich in the following dietary components can lead to better brain health?
 - **a.** Fish and seafood
 - **b.** Nuts
 - **c.** Beans
 - **d.** Whole grains
 - e. Fruits
 - f. Vegetables
- **3.** What is the best evidence that different diet patterns such as the Mediterranean diet, DASH (Dietary Approaches to Stop Hypertension), and MIND (a hybrid of the two - Mediterranean-DASH Intervention for Neurodegenerative Delay), can lead to better brain health? Does a person's age impact the efficacy of any of these diets?
- **4.** How do you encourage behavior change with respect to nutritional choices among middle age and older individuals?
 - **a.** What kind of messages and or activities might encourage sustained habits of positive dietary choices?
 - **b.** How do we most effectively convey messages regarding portion size?
- **5.** Is there evidence that specific nutrients/dietary components can lead to the delay or potentially the prevention of neurodegenerative diseases?
- **6.** What is the evidence surrounding alcohol consumption and cognitive function? Does the advice differ from recommendations surrounding wine consumption and cardiac health?

- **7.** Does the consumption of cocoa flavonoids impact cognitive function?
- **8.** What is the evidence base surrounding polyphenols in olive oil and their impact on cognitive function?
- **9.** Should adults eat less (a) meat or (b) monosaturated fats to preserve cognitive health?
- **10.** What food recommendations can you make to older adults who are seeking ways to improve cognitive function through dietary choices?
- 11. On what basis should people decide to commit to different diets? For example, juice cleanses have gained a great deal of attention in in recent years as a diet of choice for many. How does one evaluate whether a particular diet is the best one for them?
- 12. What foods should people limit? Much has been written, for example, about limiting sodium consumption. How does one strike the appropriate balance?
- **13.** Do we know anything about whether food handling and storage (i.e. canned, frozen or fresh) impacts the nutritional benefit to the brain?

4a. MyPLATE DIETARY RECOMMENDATIONS

MyPlate for Older Adults

Fruits & Vegetables

Whole fruits and vegetables are rich in important nutrients and fiber. Choose fruits and vegetables with deeply colored flesh. Choose canned varieties that are packed in their own juices or low-sodium.

Healthy Oils

Liquid vegetable oils and soft margarines provide important fatty acids and some fat-soluble vitamins.

Herbs & Spices

Use a variety of herbs and spices to enhance flavor of foods and reduce the need to add salt.



Fluids

Drink plenty of fluids. Fluids can come from water, tea, coffee, soups, and fruits and vegetables.

Grains

Whole grain and fortified foods are good sources of fiber and B vitamins.

Dairy

Fat-free and low-fat milk, cheeses and yogurts provide protein, calcium and other important nutrients.

Protein

Protein rich foods provide many important nutrients. Choose a variety including nuts, beans, fish, lean meat and poultry.



FORTIFIED CEREAL



AARP Foundation

MyPLATE FOR OLDER ADULTS OFFERS A MEMORABLE, EASY-TO-UNDERSTAND NUTRITION GUIDE.

4b. SELECT DIETARY RECOMMENDATIONS FROM GOVERNMENTS REPRESENTED BY GCBH ISSUE EXPERTS ACROSS THE GLOBE

Numerous, general dietary recommendations exist across the world. There are many features which are common to them all, and many of them are similar to the recommendations put forward by the GCBH for helping to optimize brain health. Some countries provide far more detailed guidance than others. We have provided the major recommendations from governments represented by GCBH Issue Experts below in order to provide a sample of these recommendations world-wide.

AARP is most familiar with the United States' guidelines.

DIETARY GUIDELINES FOR AMERICANS 2015-2020, A HEALTHY EATING PLAN:

- Emphasizes fruits, vegetables, whole grains, and fat-free or low-fat milk and milk products
- Includes lean meats, poultry, fish, beans, eggs, and nuts
- Is low in saturated fats, trans fats, cholesterol, salt (sodium), and added sugars
- · Stays within your daily calorie needs

U.S. Department of Health and Human Services and U.S. Department of Agriculture. 2015 – 2020 Dietary Guidelines for Americans. 8th Edition. December 2015. Available at <u>https://health.gov/</u> dietaryguidelines/2015/guidelines/.

The United States Department of Agriculture introduced the new food icon, MyPlate, to replace the MyPyramid image as the government's primary food group symbol in order to help consumers adopt healthy eating habits. While the food pyramid is something many older Americans are familiar with, the new MyPlate icon shows that the diet recommendations have changed now and are consistent with the new Dietary Guidelines for Americans.

MyPLATE FOR OLDER ADULTS

An additional healthy eating resource was created by nutrition scientists at Tufts University with support from AARP Foundation. It is based on the 2015-2020 Dietary Guidelines for Americans. The MyPlate for Older Adults Nutrition Guide can be seen in appendix 4a.

MyPLATE 10 TIPS CHOOSING HEALTHY EATING TIPS FOR PEOPLE AGE 65+

- **1.** Drink plenty of liquids
- 2. Make eating a social event
- 3. Plan healthy meals
- 4. Know how much to eat
- **5.** Vary your vegetables
- 6. Eat for your teeth and gums
- 7. Use herbs and spices
- 8. Keep food safe
- 9. Read the Nutrition Facts label

10. Ask your doctor about vitamins or supplements

CANADA

- Eat at least one dark green and one orange vegetable each day.
 - » Go for dark green vegetables such as broccoli, romaine lettuce and spinach.
 - » Go for orange vegetables such as carrots, sweet potatoes and winter squash.
- Enjoy vegetables and fruit prepared with little or no added fat, sugar or salt.
 - » Have vegetables steamed, baked or stir fried instead of deep fried.
 - » Have vegetables and fruit more often than juice.
- Make at least half of your grain products whole grain each day.
 - » Eat a variety of whole grains such as barley, brown rice, oats, quinoa and wild rice.
 - Enjoy wholegrain breads, oatmeal or wholewheat pasta.
- Choose grain products that are low in fat, sugar or salt.
 - » Compare the Nutrition Facts table on labels to make wise choices.
 - » Enjoy the true taste of grain products. When adding sauces or spreads, use small amounts.

- Drink skim, 1% or 2% milk each day.
 - » Have 500 ml (2 cups) of milk every day for adequate vitamin D.
 - » Drink fortified soy beverages if you do not drink milk.
- Select lower fat milk alternatives.
 - » Compare the Nutrition Facts table on yogurts or cheeses to make wise choices.
 - » Have meat alternatives such as beans, lentils and tofu often.
- Eat at least two food guide servings of fish each week.* Health Canada provides advice for limiting exposure to mercury from certain types of fish
 - » Choose fish such as char, herring, mackerel, salmon, sardines and trout.
- Select lean meat and alternatives prepared with little or no added fat or salt.
 - » Trim the visible fat from meats. Remove the skin from poultry.
 - » Use cooking methods such as roasting, baking or poaching that require little or no added fat.
 - » If you eat luncheon meats, sausages or prepackaged meats, choose those lower in salt (sodium) and fat.
- Enjoy a variety of foods from the four food groups.
- Satisfy thirst with water!
- Drink water regularly. It's a calorie-free way to quench your thirst. Drink more water in hot weather or when you are very active.
- Include a small amount (30–45 ml, 2–3 tbsp) of unsaturated fat each day. This includes oil used for cooking, salad dressings, margarine and mayonnaise.
 - » Use vegetable oils such as canola, olive and soybean.
 - » Choose soft margarines that are low in saturated and trans fats.
 - » Limit butter, hard margarine, lard and shortening.

CHINA

- Eat a variety of foods, mainly cereals, including appropriate amounts of whole grains.
- · Consume plenty of vegetables, fruits and tubers.
- Consume milk, beans, or dairy or soybean products every day.
- Consume appropriate amounts of fish, poultry, eggs and lean meat.
- Reduce the amount of cooking oil; choose a light diet which is also low in salt.
- Do not overeat, exercise every day, and maintain a healthy body weight.
- Logically divide the daily food intake among the three meals, and choose suitable snacks.
- Drink a sufficient amount of water every day, and select suitable beverages.
- If you drink alcoholic beverages, do so in limited amounts.
- Consume fresh and hygienic food.

ITALY

- Watch your weight and be active.
- Eat more cereals, vegetables, tubers and fruit.
- Choose high-quality fats and limit the amount you eat.
- Consume appropriate amounts of sugars, sweets and sugar-sweetened beverages.
- Drink plenty of water every day.
- Eat only small amounts of salt.
- Alcoholic drinks only if in limited amounts.
- Choose a wide variety of foods.
- Pay attention to specific advice for special people.
- The safety of your food depends also on you.

ISRAEL

- Eat a variety of foods.
- Choose different foods from each of the five major food groups every day.
- Ideally every main meal should contain at least three food groups.
- Choose fibre-containing foods such as whole grains, legumes, fruits and vegetables.
- Drink plenty of water throughout the day, including during meals.
- Choose low-fat dairy products and lean meats. Use less oil in food preparation.
- Limit your consumption of foods high in saturated fats and trans fats such as cakes and biscuits.
- Maintain a healthy body weight. Do regular physical activity.

GREECE

- Eat eight servings of non-refined cereals and products daily.
- Eat six servings of vegetables (including wild greens) daily.
- Eat three servings of fruit daily.
- Use olive oil as the main added lipid.
- · Eat two servings of dairy products a day.
- Practice physical activity on a daily basis.
- Drink wine in moderation.
- Eat five or six servings of fish a week.
- Eat four servings of poultry a week.
- Eat three or four servings of olives, pulses and nuts a week.
- Eat three servings of potatoes a week.

- Eat three servings of eggs a week.
- Eat a maximum of three servings of sweets a week.
- Eat four servings of red meat a month.
- Drink plenty of water.
- Avoid salt and replace it by herbs (e.g. oregano, basil, thyme, etc.).

SWEDEN

- More vegetables and fruit Eat lots of fruit, vegetables and berries! Ideally, choose high fibre vegs such as root vegetables, cabbage, cauliflower, broccoli, beans and onions.
- More seafood Eat fish and shellfish two to three times a week. Vary your intake of fatty and low-fat varieties, and choose eco-labeled seafood.
- More exercise Exercise for at least 30 minutes every day! Take brisk walks, for example, and reduce the amount of time you sit still by taking brief, active breaks.
- Switch to wholemeal Choose wholegrain varieties when you eat pasta, bread, grain and rice.
- Switch to healthier fat Choose healthy oils when cooking, such as rapeseed oil or liquid fats made from rapeseed oil, and healthy sandwich spreads. Look for the Keyhole symbol.
- Switch to low-fat dairy products Choose low-fat, unsweetened products enriched with vitamin D.
- Less red and processed meat Eat less red and processed meat, no more than 500 grams a week. Only a small amount of this should be processed meat.
- Less salt Choose food with less salt. Use less salt when you cook, but choose salt with iodine when you do use it.
- Less sugar Hold back on the sweets, pastries, ice creams and other products containing lots of sugar. Cut back on sweet drinks in particular.
- Maintain a balance Try to maintain energy balance by eating just the right amount.

UNITED KINGDOM

- Eat at least 5 portions of a variety of fruit and vegetables every day.
- Base meals on potatoes, bread, rice, pasta or other starchy carbohydrates; choosing wholegrain versions where possible.
- Have some dairy or dairy alternatives (such as soya drinks); choosing lower fat and lower sugar options.
- Eat some beans, pulses, fish, eggs, meat and other proteins (including 2 portions of fish every week, one of which should be oily).
- Choose unsaturated oils and spreads and eat in small amounts.
- Drink 6-8 cups/glasses of fluid a day.

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

	EPIDEMIOLOGICAL (OBSERVATIONAL) STUDIES	RANDOMIZED CONTROLLED TRIALS (RCTS)
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 which 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	 Usually larger number of people. Can take into account influences from many more factors and personal characteristics and disease states. Can assess many dose levels and durations of behavior. Can detect slow or cumulative changes over time. 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. 	 Helps to prove causal link and to better understand mechanisms. Randomization can eliminate many competing hypotheses as why the change actually happened (because confounding factors have an equal probability of occurring in all groups). Can test whether different dose of the intervention (e.g., exercise frequency, drug dose) can lead to different outcomes. Uses detailed and objective measurements and assessments.

- Does not prove any specific causal link.
- May not capture all characteristics which influence health.
- Any characteristic may reflect another more important factor (e.g., people who take expensive medications may have better access to health care).
- Selective drop-out of those less socially advantaged and less healthy.
- Difficult to generalize from one region to another due to differences in diet, environment, healthcare, etc.
- Often cannot collect detailed information due to the large numbers of participants and measures.
- Expensive to set up and run, especially over long periods.
- Some studies rely on self-reported behavior which may be inaccurate.
- People who partake in a study to be followed for long periods of time might bias inclusion.

- Usually smaller number of people.
- While an RCT attempts to control for confounding factors, it may not capture all characteristics which influence health.
- The study may be too limited in size or duration to detect subtle effects.
- Difficult to test conditions which scientists cannot change (e.g., gender, genetics, past exposure).
- Difficult to generalize from one region to another due to differences in diet, environment, healthcare, etc...
- 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.
- Effects are restricted to defined dose and intervention type.
- RCTs usually have very strict inclusion and exclusion criteria so the samples are often unrepresentative and results cannot be as widely generalized.
- Attrition rate during the course of the RCT could bias the results.
- Outcome reporting bias can influence results in which primary outcomes are changed, introduced or omitted since the original protocol.
- 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.

6. DISCLOSURE STATEMENT OF POTENTIAL FINANCIAL CONFLICTS OF INTEREST

All of the twenty-four GCBH experts participating in the formulation of this paper were asked to disclose potential conflicts of interest. Twenty of the experts who participated in the meeting and contributed to the formulation of the recommendations attested they had no conflicts of interest. Four of the experts disclosed ongoing relationships which have the potential to raise perceived financial conflicts of interest involving for-profit companies. Dr. Petersen declared part-time consultation with several pharmaceutical companies. Dr. Troen is coinventor on a patent for a neuroprotective natural extract product. Dr. Okereke disclosed publishing royalties for a book on late-life depression prevention. Dr. Estep is the founder and equity stakeholder in Veritas Genetics. These disclosures are available upon request by contacting staff of the Global Council on Brain Health.

7. FUNDING

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 September 11-13, 2017 and for the participation of the Governance Committee members in conference calls. Liaisons did not receive reimbursement or honoraria.

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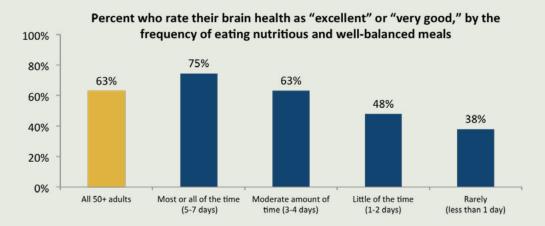
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9. FIGURES

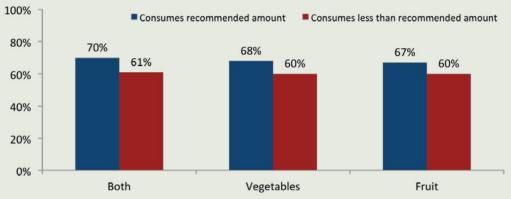
FIGURE 1



Those who report eating a healthy diet report better brain health. Adults age 50 and older who eat healthy are twice as likely to report their brain health as "excellent" or "very good" compared to those who said they do not eat a healthy diet. (75% vs. 38%).

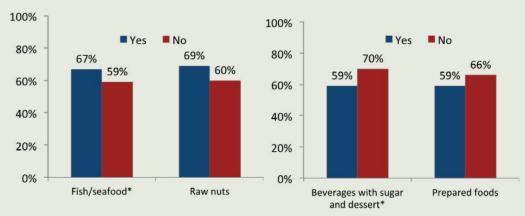
FIGURE 2

Percent who rate their brain health as "excellent" or "very good," by the consumption of recommended amounts of fruits and vegetables



Significantly more adults age 50 and older who eat the recommended* amounts of fruits and vegetables report better brain health.

*Recommended amount per day is based on USDA recommendations (<u>www.myplate.gov</u>). Recommendations vary by age and gender.



Percent who rate their brain health as "excellent" or "very good," by the consumption of certain foods in a typical week

Adults age 50 and older who eat healthier foods are significantly more likely to report their brain health as "excellent" or "very good." Conversely, adults who consume less-healthy foods are less likely to report their brain health as "excellent" or "very good."

*Items were combined.

NOTES





The Real Deal on Brain Health Supplements:

GCBH Recommendations on Vitamins, Minerals, and Other Dietary Supplements



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.

Acknowledgments: AARP Policy, Research and International; AARP Integrated Communications and Marketing. Suggested Citation: Global Council on Brain Health (2019). "The Real Deal on Brain Health Supplements: GCBH Recommendations on Vitamins, Minerals, and Other Dietary Supplements." Available at <u>www.GlobalCouncilOnBrainHealth.org</u>. DOI: <u>https://doi.org/10.26419/pia.00094.001</u>.

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.' 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 alphalinoleic 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

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.

^{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

FOR INDIVIDUALS:

- Rather than turning to supplements to boost brain health, choose foods known to support a healthy brain. See *Brain Food:* <u>GCBH Recommendations on</u> <u>Nourishing Your Brain Health</u> 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.

FOR HEALTH CARE PROVIDERS:

 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.

- **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.
- **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:

- 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 <u>GCBH reports</u> 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

<u>Brain-Sleep Connection</u>" 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

- **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, <u>www.consumerlab.com</u>
 - b. NSF International, www.nsf.org
 - c. U.S. Pharmacopeia (USP), 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

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 <u>Office</u> <u>of Dietary Supplements</u>, the <u>Alzheimer's Drug Discovery</u> <u>Foundation</u>, <u>Cognitive Vitality</u> and <u>ConsumerLab.com</u>.

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 <u>globalcouncilonbrainhealth.org</u>.

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 wome	en 600 mcg DFE
Breastfeeding teens and v	vomen 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' <u>fact sheet on vitamin D</u> and Cognitive Vitality's <u>vitamin D rating</u>.

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	

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 agerelated 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 anxioxidants 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 "<u>The Brain-Sleep Connection</u>." 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 <u>Brain Food:</u> <u>GCBH Recommendations on Nourishing Your Brain</u> <u>Health</u>.

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 place 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 <u>fda.gov/ICECI/EnforcementActions/</u> <u>WarningLetters/ucm630531.htm</u>

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 <u>fda.gov/ICECI/</u> <u>EnforcementActions/WarningLetters/ucm630558.htm</u>

Prescription drug for Alzheimer's/Parkinson's. Warning letter sent for unsubstantiated claim available at <u>fda.gov/ICECI/</u> EnforcementActions/WarningLetters/ucm630486.htm Supplementation shown to reduce risk of Alzheimer's Disease. Warning letter sent for unsubstantiated claim available at <u>fda.gov/ICECI/EnforcementActions/WarningLetters/</u> <u>ucm630486.htm</u>

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 <u>fda.gov/ICECI/EnforcementActions/</u> WarningLetters/ucm630570.htm

The FTC press release, with links to specific letters sent by FTC is available here: <u>ftc.gov/news-events/blogs/business-blog/2019/02/ftc-fda-warning-letters-target-treatment-claims-alzheimers</u>

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 wellbeing. 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:

 $\underline{cancer.org/treatment/treatments-and-side-effects/complementary-and-alternative-medicine/dietary-supplements/fda-regulations.html.$

KNOWLEDGE GAPS: WHERE MORE RESEARCH IS NEEDED

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 supplements 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 highquality 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 wellknown 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 longterm 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 or 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: <u>GlobalCouncilonBrainHealth.org</u>.

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
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Participants' and Liaisons' List of Additional Resources

Cognitive Vitality: alzdiscovery.org/cognitive-vitality

ConsumerLab.com: consumerlab.com

Description of EU Regulations: efsa.europa.eu/en/topics/topic/ food-supplements

Description of UK Regulations: food.gov.uk/sites/default/ files/media/document/ foodsupplementsenglish_o.pdf

Federal Trade Commission— Information on how to report how to report a concern about a supplement: <u>consumer.ftc.</u> <u>gov/blog/2017/07/dietary-</u> <u>supplement-concerns-tell-ftc-</u> <u>and-fda</u>

FTC press release following recent enforcement actions: <u>ftc.</u> <u>gov/news-events/blogs/businessblog/2019/02/ftc-fda-warningletters-target-treatment-claimsalzheimers</u>

Office of Dietary Supplements: ods.od.nih.gov

United States Food and Drug Administration: <u>fda.gov</u>

United States Government Accountability Office report to Senators McCaskill and Casey, October 18, 2018: <u>https://www.</u> <u>gao.gov/assets/700/695049.pdf</u>

United States Pharmacopeia: 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

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 wellbeing.

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 batchto-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

- 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	 Usually larger number of people Can take into account influences from many more factors and personal characteristics and disease states Can assess many dose levels and durations of behavior Can detect slow or cumulative changes over time 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 	 Helps to prove causal link and to better understand mechanisms Randomization can eliminate many competing hypotheses as why the change actually happened (because confounding factors have an equal probability of occurring in all groups) Can test whether different dose of the intervention (e.g., exercise frequency, drug dose) can lead to different outcomes Uses detailed and objective measurements and assessments
Limitations	 Does not prove any specific causal link. May not capture all characteristics that influence health. Any characteristic may reflect another more important factor (e.g., people who take expensive medications may have better access to health care). Selective drop-out of those less socially advantaged and less healthy. Difficult to generalize from one region to another due to differences in diet, environment, health care, etc. Often cannot collect detailed information due to the large numbers of participants and measures. Expensive to set up and run, especially over long periods. Some studies rely on self-reported behavior which may be inaccurate. People who partake in a study to be followed for long periods of time might bias inclusion. 	 Usually smaller number of people While an RCT attempts to control for confounding factors, it may not capture all characteristics which influence health. The study may be too limited in size or duration to detect subtle effects. Difficult to test conditions which scientists cannot change (e.g., gender, genetics, past exposure) Difficult to generalize from one region to another due to differences in diet, environment, health care, etc. 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. Effects are restricted to defined dose and intervention type. RCTs usually have very strict inclusion and exclusion criteria, so the samples are often unrepresentative and results cannot be as widely generalized. Attrition rate during the course of the RCT could bias the results. Outcome reporting bias can influence results in which primary outcomes are changed, introduced or omitted since the original protocol. 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.

5. DISCLOSURE STATEMENT OF POTENTIAL FINANCIAL CONFLICTS OF INTEREST

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

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.

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SAVE YOUR MONEY, HONEY!

The GCBH does not recommend any dietary supplement for brain health.*

6 Things to Consider Before You Buy a Supplement

Beware of supplement claims that sound too good to be true.

Show your health care provider what drugs & supplements you're already taking. They may interact with each other. **Check for warnings** related to your specific health conditions and for third-party quality assurance.

Think about whether you're already getting enough of a nutrient through your diet before you buy.

Food is better than pills to get the nutrition you need to help your brain.

Make sure you **don't take more of a supplement than is recommended**; more is not always better.



*Unless you are one of the relatively few people in the U.S. with a vitamin B12/folate deficiency. It is estimated that 4.4% of US. adults 50+ are low on vitamin B12, but even fewer are low on folate. See Evatt, M.L. et al. (2010) "Association between vitamin B12- containing supplement consumption and prevalence of biochemically defined B12 deficiency in NHANES III (Third National Health and Nutrition Survey)." Public Health Nutr.: 13(1), 25–31. See also https://www.cdc.gov/nutritionreport/pdf/Second-Nutrition-Report-Overview-Factsheet.pdf

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For more brain health tips see stayingsharp.org DOI: (https://doi.org/10.26419/pia.00094.002)

