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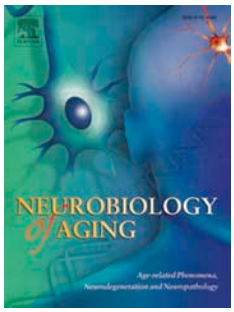
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Dietary and Lifestyle Guidelines for the Prevention of Alzheimer's Disease

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Abstract

Risk of developing Alzheimer's disease is increased by older age, genetic factors, and several medical risk factors. Studies have also suggested that dietary and lifestyle factors may influence risk, raising the possibility that preventive strategies may be effective. This body of research is incomplete. However, because the most scientifically supported lifestyle factors for Alzheimer's disease are known factors for cardiovascular diseases and diabetes, it is reasonable to provide preliminary guidance to help individuals who wish to reduce their risk. At the International Conference on Nutrition and the Brain, Washington, DC, July 19-20, 2013, conference speakers were asked to comment on possible guidelines for Alzheimer's disease prevention, with an aim of developing a set of practical, albeit preliminary, steps to be recommended to members of the public. From this discussion, 7 guidelines emerged related to healthful diet and exercise habits.

1. Introduction

Alzheimer's disease affected an estimated 4.7 million Americans in 2010, and its prevalence is expected to nearly triple in coming decades (Hebert 2013). Several factors contribute to the risk of developing late-onset Alzheimer's disease, including older age, genetic factors (especially the presence of the APOEε4 allele), family history, and a history of head trauma, as well as midlife hypertension, obesity, diabetes, and hypercholesterolemia (Bendlin 2010).

In addition, recent prospective studies have shown that certain dietary and lifestyle factors, including saturated fat intake, vitamin E intake, and physical exercise, among others, are associated with Alzheimer's risk, suggesting that prevention strategies may be applicable for these factors. In each of these areas, scientific evidence is less than complete. Nonetheless, individuals at risk for Alzheimer's disease make decisions about dietary and lifestyle on a daily basis and need to act on the best evidence available to them, even when scientific consensus may not have been achieved.

In toxicology, the *precautionary principle* is invoked in situations in which there is a substantial basis for concern regarding the health consequences of an exposure and for which available data preclude a comprehensive evaluation of risk (European Commission 2000). A similar approach can be applied to nutritional and other lifestyle-related exposures, particularly for conditions, such as cancer or Alzheimer's disease, for which there may be a long latency period between exposure and disease manifestation and for which randomized controlled trials are impractical or are, for whatever reason, not rapidly forthcoming. Some have argued that the level of evidence required for

making dietary recommendations for disease prevention may be different from that required for establishing the efficacy of medical treatments, such as pharmaceuticals. (Blumberg 2010).

At the International Conference on Nutrition and the Brain, Washington, DC, July 19-20, 2013, evidence regarding the influence of dietary factors as well as physical and mental exercise and sleep on aspects of cognition was reviewed, and conference speakers were asked to comment on possible dietary and lifestyle guidelines for Alzheimer's disease prevention, with an aim of developing a set of practical steps to be recommended to members of the public.

2. Methods

The following principles were applied to the development of guidelines:

1. Guidelines were to be based on substantial, although not necessarily conclusive, evidence of benefit.
2. Implementation of guidelines should present no reasonable risk of harm.
3. The guidelines were to be considered to be subject to modification as scientific evidence evolves.

3. Results

Seven guidelines emerged and are as follows:

1. Minimize your intake of saturated fats and trans fats. Saturated fat is found primarily in dairy products, meats, and certain oils (coconut and palm oils). Trans fats are found

in many snack pastries and fried foods and are listed on labels as “partially hydrogenated oils.”

2. Vegetables, legumes (beans, peas, and lentils), fruits, and whole grains should replace meats and dairy products as primary staples of the diet.

3. Vitamin E should come from foods, rather than supplements. Healthful food sources of vitamin E include seeds, nuts, green leafy vegetables, and whole grains. The RDA for vitamin E is 15 mg per day.

4. A reliable source of vitamin B12, such as fortified foods or a supplement providing at least the recommended daily allowance (2.4 mcg per day for adults) should be part of your daily diet. Have your blood levels of vitamin B12 checked regularly as many factors, including age, impair absorption.

5. If using multiple vitamins, choose those without iron and copper, and consume iron supplements only when directed by your physician.

6. While aluminum’s role in Alzheimer’s disease remains a matter of investigation, those who desire to minimize their exposure can avoid the use of cookware, antacids, baking powder, or other products that contain aluminum.

7. Include aerobic exercise in your routine, equivalent to 40 minutes of brisk walking three times per week.

4. Discussion

The rationale for each of these guidelines is briefly discussed below.

1. Minimize your intake of saturated fats and trans fats.

As reviewed elsewhere in this supplement, several (although not all) prospective studies have indicated an association between intake of saturated or trans fats and incident Alzheimer's disease (Morris 2014, Barnard 2014). Saturated fat is found especially in dairy products and meats; trans fats are found in many snack foods.

In the Chicago Health and Aging Project, individuals in the upper quintile of saturated fat intake had twice the risk of developing Alzheimer's disease during a four-year study period, compared with participants in the lowest quintile (Morris 2003). In the Washington Heights–Inwood Columbia Aging Project in New York and the Cardiovascular risk factors, Aging and Dementia (CAIDE) study in Finland, Alzheimer's disease risk was positively, but non-significantly, associated with saturated fat intake (Luchsinger 2002, Laitinen 2006). A number of well-controlled studies of cognitive decline have found that high saturated fat intake increases the rate of decline in cognitive abilities with age (Heude 2003, Morris 2006b, Beydoun 2007, Eskelinen 2008, Devore 2009, Okereke 2012).

Increased saturated fat intake is associated with risk of cardiovascular disease and type 2 diabetes (Mann 2002, Mahendran 2013), which, in turn, are associated with

increased risk of Alzheimer's disease (Puglielli 2003, Ohara 2011). A large study of Kaiser Permanente patients showed that participants with total plasma cholesterol levels ≥240 mg/dl in mid-life had a 57 percent higher risk of Alzheimer's disease three decades later, compared with participants with cholesterol levels <200 mg/dl (Solomon 2009).

Additional evidence of mechanistic associations between saturated or trans fat intake and Alzheimer's risk comes from the fact that the APOEε4 allele, which is strongly linked to Alzheimer's risk, produces a protein that plays a key role in cholesterol transport (Puglielli 2003) and from the observation that high-fat foods and/or the increases in blood cholesterol concentrations they may cause may contribute to beta-amyloid production or aggregation in brain tissues (Puglielli 2001).

2. Vegetables, legumes (beans, peas, and lentils), fruits, and whole grains should replace meats and dairy products as primary staples of the diet.

Vegetables, berries, and whole grains provide healthful micronutrients important to the brain and have little or no saturated fat or trans fats. In both the Chicago Health and Aging Project and the Nurses' Health Study cohorts, high vegetable intakes were associated with reduced cognitive decline (Morris 2006a, Kang 2005). Legumes and fruits merit emphasis, not because of an association with reduced Alzheimer's disease risk, but because, like grains and vegetables, they provide macronutrient nutrition that is essentially free of saturated and trans fats and are part of a dietary pattern associated with reduced risk of cardiovascular disease, weight problems, and type 2 diabetes (Fraser 2009, Tonstad 2009), which, in turn, have critical influences on brain health.

Many plant-based foods are rich in several B-vitamins. Folate and vitamin B6 are noteworthy in that, along with vitamin B12, they act as co-factors for the methylation of homocysteine; elevated homocysteine levels are associated with higher risk of cognitive impairment in some studies (Vogel 2009, Morris 2012, Smith 2010). Nonetheless, the efficacy of B-vitamins is not yet settled; in an Oxford University study of older individuals with elevated homocysteine levels and mild cognitive impairment, supplementation with these three vitamins maintained memory performance and reduced the rate of brain atrophy (Smith 2010, de Jager 2012, Douaud 2013).

Healthful sources of folate include leafy green vegetables, such as broccoli, kale, and spinach, as well as beans, peas, citrus fruits, and cantaloupe. The recommended dietary allowance (RDA) for folic acid in adults is 400 micrograms per day. Vitamin B6 is found in green vegetables in addition to beans, whole grains, bananas, nuts, and sweet potatoes. The RDA for adults up to age 50 is 1.3 milligrams per day. For adults over 50, the RDA is 1.5 milligrams for women and 1.7 milligrams for men.

3. Vitamin E should come from foods, rather than supplements. Healthful food sources of vitamin E include seeds, nuts, green leafy vegetables, and whole grains. The RDA for vitamin E is 15 mg per day.

In the Chicago Health and Aging Project, higher intakes of vitamin E from food sources were associated with reduced Alzheimer's disease incidence (Morris 2005). Similarly, in the Rotterdam study, high vitamin E intake was associated reduced dementia incidence. (Devore 2010).

Vitamin E occurs naturally in the form of tocopherols and tocotrienols and is found in many foods, including mangoes, papayas, avocadoes, tomatoes, red bell peppers, and spinach, and in particularly high quantities in nuts, seeds, and oils. The RDA for adults is 15 milligrams. A small handful of typical nuts or seeds contains about 5 mg of vitamin E.

Vitamin E from supplements has not been shown to reduce Alzheimer's disease risk. Many common supplements provide only α-tocopherol, and most do not replicate the range of vitamin E forms found in foods. A high intake of α-tocopherol has been shown to reduce serum concentrations of γ- and δ-tocopherol (Huang 2003).

4. A reliable source of vitamin B12, such as fortified foods or a supplement providing at least the recommended dietary allowance (2.4 mcg per day for adults) should be part of your daily diet. Have your blood levels of vitamin B12 checked regularly as many factors, including age, impair absorption.

Vitamin B12 is essential for the health of the brain and nervous system and for blood cell formation. The RDA for adults is 2.4 micrograms. It is found in supplements and fortified foods, such as some breakfast cereals or plant milks. Vitamin B12 is also found in meats and dairy products, although absorption from these sources is limited in many individuals, particularly those over age 50, those with reduced stomach acid production, those taking certain medications (eg, metformin and acid-blockers), and individuals who have had gastrointestinal surgery (eg, bariatric surgery) or who have Crohn's disease or celiac disease.

The U.S. Government recommends that vitamin B12 from supplements or fortified foods be consumed by all individuals over age 50. Individuals on plant-based diets or with absorption problems should take vitamin B12 supplements regardless of age. However, dietary sources and even vitamin B12 supplements may not be sufficient to sustain adequate blood levels. Some individuals require vitamin B12 injections. Every middle-aged or older adult should have his or her vitamin B12 status checked on a regular basis.

5. If using multiple vitamins, choose those without iron and copper, and consume iron supplements only when directed by your physician.

Iron is essential for formation of hemoglobin and certain other proteins, and copper plays an essential role in enzyme functions among many other aspects of health. However, some studies have suggested that excessive iron and copper intake may contribute to cognitive problems for some individuals (Brewer 2009, Stankiewicz 2009, Squitti 2014). In recent meta-analyses (Squitti 2013, Schrag 2013; Ventriglia 2012), circulating non-protein-bound copper was associated Alzheimer's disease risk.

Other aspects of the diet may play a modulating role in the relationship between metals and cognitive effects. In the Chicago Health and Aging Project, individuals with a high intake of saturated fat along with a high copper intake were found to have cognitive decline equivalent to 19 additional years of aging (Morris 2006b).

Most common multivitamins contain both iron and copper, sometimes exceeding the RDA (Physicians Committee for Responsible Medicine 2013). However, most individuals in the U.S. meet the recommended intake of these minerals from everyday

foods and do not require supplementation. The RDA for iron for women older than 50 and for men at any age is 8 milligrams daily. For women ages 19 to 50 the RDA is 18 milligrams. The RDA for copper for men and women is 0.9 milligrams per day. For individuals who use multiple vitamins, it is prudent to favor products that deliver vitamins only, unless specifically directed by one's personal physician. Some authorities also suggest specific clinical testing (for example, to measure levels of non-ceruloplasmin copper) before initiating diet changes (Squitti 2014).

6. While aluminum's role in Alzheimer's disease remains a matter of investigation, those who desire to minimize their exposure can avoid the use of cookware, antacids, baking powder, or other products that contain aluminum.

Aluminum's role in Alzheimer's disease remains controversial. Some researchers have called for caution, citing aluminum's known neurotoxic potential when entering the body in more than modest amounts (Kawahara 2011) and the fact that aluminum has been demonstrated in the brains of individuals with Alzheimer's disease (Crapper 1973, Crapper 1976). Studies in the United Kingdom and France found increased Alzheimer's prevalence in areas where tap water contained higher aluminum concentrations (Martyn 1989, Rondeau 2009). However, due to the limited number of relevant studies, most experts regard current evidence as insufficient to indict aluminum as a contributor to Alzheimer's disease risk.

Because aluminum plays no role in human biology, it may be prudent to avoid aluminum exposure to the extent possible while its role in cognitive disorders remains

under investigation. Aluminum is found in some brands of baking powder, antacids, certain food products, and antiperspirants.

7. Include aerobic exercise in your routine, equivalent to 40 minutes of brisk walking three times per week.

Observational studies have shown that individuals who exercise regularly are at reduced risk for Alzheimer's disease (Erickson 2012). Adults who exercised in midlife were found to be less likely to develop dementia after age 65, compared with their sedentary peers (DeFina 2013). In controlled trials, aerobic exercise—such as brisk walking for 40 minutes three times per week—reduces brain atrophy and improves memory and other cognitive functions (Hotting 2013).

In addition to the foregoing guidelines, other steps merit further investigation for possible inclusion in future iterations of prevention guidelines. These could include recommendations to:

1. Maintain a sleep routine that will provide an appropriate amount of sleep each night, approximately 7-8 hours for most individuals. It is important to evaluate and treat any underlying sleep disorders, such as obstructive sleep apnea. Sleep disturbances have been associated with cognitive impairment in older adults (Tworoger 2006, Blackwell 2011, Yaffe 2011, Lim 2013).

2. Engage in regular mental activity that promotes new learning, for example, 30 minutes per day, 4-5 times per week. Several studies have suggested that

individuals who are more mentally active have reduced risk for cognitive deficits later in life (Robertson 2013, Tucker 2011, Stern 2012, Hotting 2013, Curlik 2013).

5. Conclusion

Although current scientific evidence is incomplete, substantial evidence suggests that, a combination of healthful diet steps and regular physical exercise may reduce the risk of developing Alzheimer's disease. These lifestyle changes present additional benefits, particularly for body weight, cardiovascular health, and diabetes risk, and present essentially no risk of harm. As investigations into Alzheimer's disease bear additional fruit, these guidelines should be modified accordingly.

Disclosure statement

Dr. Barnard writes books and articles and gives lectures related to nutrition and health, and has received royalties and honoraria from these sources. He and Susan Levin are affiliated with the Physicians Committee for Responsible Medicine, which promotes the use of low-fat, plant-based diets and discourages the use of animal-derived, fatty, and sugary foods. Dr. Bush is a shareholder in Cogstate Ltd, Prana Biotechnology Ltd and Mesoblast Pty Ltd. Dr. de Jager has received honoraria from the Institute of Life Sciences Europe (ILSI) to contribute to manuscripts for publication, as well as travelling expenses for meetings while on their nutrition and cognition expert group and task force, and from the Chinese Nutrition Society for a conference presentation. Dr. Kesler writes books and gives lectures regarding cognitive exercise and cognitive reserve and

has received royalties and honoraria from these sources. All authors other than Dr. Barnard and Ms. Levin received honoraria from the Physicians Committee for Responsible Medicine for oral presentations at the International Conference on Nutrition and the Brain. Drs. Ceccarrelli, Cooper, Erickson, Fraser, Kesler, Lucey, Morris, and Squitti reported no other dualities of interest.

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