

Integrative Medicine

Evidence-based summaries and critical reviews on
the latest developments in integrative therapies [ALERT]

SUPPLEMENTS

ABSTRACT & COMMENTARY

Trends in Supplemental Vitamin D Intake

By *Traci Pantuso, ND, MS*

Adjunct Faculty, Research Investigator, Bastyr University, Seattle

Dr. Pantuso reports no financial relationships relevant to this field of study.

SYNOPSIS: The authors investigated the trends in daily supplemental vitamin D intake of $\geq 1,000$ IU and $\geq 4,000$ IU and found increasing use of vitamin D supplementation.

SOURCE: Rooney MR, Harnack L, Michos ED, et al. Trends in use of high-dose vitamin D supplements exceeding 1000 or 4000 International Units daily, 1999-2014. *JAMA* 2017;317:2448-2450.

Vitamin D is a fat-soluble vitamin that either is consumed through dietary sources or synthesized when skin is exposed to ultraviolet light.¹ The benefits of adequate vitamin D intake are well demonstrated in the skeletal system, as severe vitamin D deficiency results in rickets in children and osteomalacia in adults.^{1,2} The role of vitamin D in extraskeletal health is not well understood, and the majority of evidence to support its use is from association and observational studies.^{1,3,4}

Some consider hypovitaminosis D, which is caused by low levels of vitamin D naturally

occurring in foods and a lack of sufficient sunlight exposure, to be a pandemic worldwide.⁵ Individuals with increased melanin in their skin and those who use sunblock have decreased vitamin D synthesis resulting from sunlight exposure.^{4,5} Because of inadequate dietary intake of vitamin D and decreased synthesis from sunlight exposure, many individuals require oral vitamin D supplementation.¹⁻⁸

To assess the changes in vitamin D intake from 1999 to 2014 and investigate trends of use, Rooney et al used repeat cross-sectional data from the National Health and Nutrition

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Summary Points

- The number of U.S. adults consuming daily vitamin D supplements of $\geq 1,000$ IU and $\geq 4,000$ IU increased between 1999 and 2014.
- Eighteen percent of individuals were taking more than 1,000 IU of vitamin D per day and 3% of individuals were exceeding 4,000 IU of vitamin D per day, which is above the tolerable upper intake level.

Examination Survey (NHANES), which samples U.S. residents who are not institutionalized. The authors excluded participants who were pregnant, were younger than 20 years of age, or for whom incomplete information about supplement use was available. Participants self-reported vitamin D supplement use for 30 days. They were asked to bring in supplement bottles to aid in reporting. Vitamin D supplementation of $\geq 1,000$ IU and $\geq 4,000$ IU was calculated for each NHANES survey period. The researchers used Stata to analyze the data and calculated linear trends. A two-sided *P* value of < 0.05 was considered statistically significant.

The study included 39,243 participants, with a mean age of 46.6 years (standard deviation = 16.8), 51.1% women, and 69.7% self-reported as non-Hispanic white. A significant difference was found in the prevalence of vitamin D use of 1,000 IU per day between 1999-2000 and 2013-2014. Use of vitamin D $\geq 1,000$ IU in 2013-2014 was significantly higher at 18.2% (95% confidence interval [CI], 16.0-20.7%) compared to 1999-2000, when use was 0.3% (95% CI, 0.1-0.5%; *P* for trend < 0.001). The use of $\geq 4,000$ IU vitamin D prior to 2005-2006 was $< 0.1\%$ and was 3.2% (95% CI, 2.5-4.0%) in 2013-2014.

The authors did not differentiate between vitamin D2 and vitamin D3 supplements. The increases in vitamin D supplement intake were found in most age groups, races/ethnicities, and both sexes. The use of $\geq 1,000$ IU in 2013-2014 was highest in women (25.9%; 95% CI, 22.8-29.3%), non-Hispanic white individuals (21.8%; 95% CI, 19.3-24.6%), and individuals who were 70 years of age or older (38.5%; 95%

CI, 31.8-45.7%). The use of $\geq 4,000$ IU in 2013-2014 was highest in women (4.2%; 95% CI, 3.0-5.7%), non-Hispanic white individuals (3.9%; 95% CI, 3.0-5.1%), and individuals who were 70 years of age or older (6.6%; 95% CI, 4.2-10.2%).

■ COMMENTARY

Rooney et al found that U.S. adults are supplementing with increasing amounts of vitamin D, and that this increase is highest in non-Hispanic white women older than 70 years of age. Three percent of the population studied exceeded the 4,000 IU tolerable upper limit, and 18% exceeded 1,000 IU per day.

The recommended dietary allowance (RDA) of vitamin D is 600 IU/day for those between 1 and 70 years of age and 800 IU/day for adults 71 years of age and older.¹ The American Academy of Pediatrics recommends 400 IU/day for children younger than 1 year of age.⁶

Over the course of the study period, there was a marked increase in the use of vitamin D supplements at the two doses documented. The authors did not discuss potential reasons or theories behind the increase in supplemental vitamin D intake. However, in 2017, the vitamin D industry was estimated to be worth \$936 million.⁹ Currently, serum vitamin D levels are the fifth most commonly ordered lab tests covered by Medicare.⁹ Serum vitamin D tests increased 80-fold between 2000 and 2010, most likely because of increasing knowledge of diseases that potentially could be associated with low vitamin D levels.¹⁰

There are many purported uses for vitamin D; it is generally accepted that vitamin D is important physiologically.

For example, the National Academy of Medicine (NAM), formerly the Institute of Medicine, concluded that vitamin D was beneficial for bone health. However, evidence is insufficient for extraskelatal health recommendations. Rather than focus on supplementation or dietary recommendations, there is some thought that vitamin D status, as determined by serum levels, is the important variable. On this note, NAM concluded that a serum vitamin D (25(OH)D) level < 12 ng/mL is indicative of being at risk for vitamin D deficiency. In addition, some people may be at risk for vitamin D deficiency at serum 25(OH)D levels between 12-20 ng/mL. For most people, a serum 25(OH)D level of 20 ng/mL or higher is recommended. A 25(OH)D serum level > 50 ng/mL is associated with adverse events. Although 25(OH)D serum levels indicate exposure to vitamin D, they do not measure body storage of vitamin D and have not been shown to be a reliable marker for health outcomes.¹

Although Rooney et al found an increasing use of supplemental vitamin D in the U.S. population, it also is possible to obtain vitamin D through diet. Few unfortified foods contain adequate amounts of vitamin D naturally. Fatty fish and fatty fish oils contain vitamin D3, and small amounts of vitamin D3 can be found in egg yolks, cheese, and beef liver.⁷ Mushrooms contain vitamin D2 and may contain increased amounts of vitamin D2 if exposed to light.⁷ Vitamin D needs also can be met through exposure to sunlight. However, cloud cover can reduce ultraviolet energy by 50%, and ultraviolet B radiation, which is required for vitamin D3 synthesis, is unable to penetrate glass.²

This study had a number of strengths, including a large number of participants and the NHANES response rate of 74%. Study limitations include the lack of representation of diverse races and ethnicities, as 69.7% self-reported as non-Hispanic white, and the mean age was 46.6 years old.

Another major limitation of this study is that many vitamin D supplements have been found to exceed their vitamin D label claims. According to Labdoor, a company that tests supplements, an analysis of 19 of the best-selling vitamin D supplements in the United States found that all of the products exceeded their vitamin D label claims by 22%, and six products exceeded their label claims by 40%.¹¹ Multivitamins usually contain label claims of 400 IU/day. Vitamin D intakes > 1,000 IU per day may indicate additional supplemental vitamin D intake. Furthermore, no distinction was made between different formulations of vitamin D (i.e., vitamin D2 vs.

vitamin D3). There may be variable physiological effects between these supplements.⁵

Since some participants' vitamin D intakes exceeded the RDA, there might be concerns about vitamin D toxicity. Gailor et al reviewed case reports of vitamin D toxicity, which included information about how much vitamin D was being taken, the serum vitamin D level at the time of admission, and a complete medical evaluation.¹⁰ They found that most cases of vitamin D toxicity are due to intake of vitamin D supplements that exceed their label claims.¹⁰ The authors found

[Although reports of vitamin D toxicity appear to be rare, the increase in use of vitamin D supplements may increase adverse events. Unfortunately, supplemental vitamin D label claims do not always reflect the actual concentration in the supplement, making it difficult to recommend vitamin D supplements.]

that serum levels > 150 ng/mL posed toxicity risks and should be avoided.¹⁰ Vitamin D intoxication leads to hypercalcemia through increased calcium absorption in the gut and hypercalciuria. The increased calcium levels also may lead to muscle weakness, hypertension, neuropsychiatric symptoms, renal toxicity, and renal calculi.¹⁰ Of note, the official upper level is 4,000 IU in adults and children 9 years of age and older.

Although reports of vitamin D toxicity appear to be rare, the increase in use of vitamin D supplements may increase adverse events. Unfortunately, supplemental vitamin D label claims do not always reflect the actual concentration in the supplement, making it difficult to recommend vitamin D supplements. Certain populations are at risk of vitamin D deficiency, including breastfed infants, people with limited sun exposure, people with dark skin, older adults, people with decreased fat absorption, individuals with inflammatory bowel disease, people with obesity, and those who have undergone gastric bypass surgery.^{1,2,3,6,8} Although serum 25(OH)D levels are the best indicator of

vitamin D status, they are not indicative of storage levels of vitamin D in tissue.^{4,5,7}

Patients are taking vitamin D supplements, so it is important for providers to obtain accurate lists of supplements they are taking. In patients at risk for vitamin D deficiency, obtaining a serum 25(OH)D level may be helpful when recommending adequate amounts of vitamin D through diet, sun exposure, and multivitamin or supplement use. Providers should monitor serum 25(OH)D levels during treatment to ensure that supplementation is not excessive. In all patients, especially those at risk for adverse events due to high intake of vitamin D supplements, education about the inaccuracy of label claims of many vitamin D supplements and risks of toxicity is important. ■

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ALZHEIMER'S DISEASE

ABSTRACT & COMMENTARY

Effect of Diet on Hippocampal Volume in a Population at Risk for Alzheimer's Disease

By Lisa Mosconi, PhD

Associate Director, Alzheimer's Prevention Clinic/Department of Neurology, Weill Cornell Medical College

Dr. Mosconi reports no financial relationships relevant to this field of study.

SYNOPSIS: Magnetic resonance imaging of the brain in community-dwelling people (average age of 60 years) found that a long-term, high-quality diet was associated with larger hippocampal volumes after an average interval of 11 years.

SOURCE: Akbaraly T, Sexton C, Zsoldos E, et al. Association of long-term diet quality with hippocampal volume: Longitudinal cohort study. *Am J Med* 2018; Jul 26. doi: 10.1016/j.amjmed.2018.07.001. [Epub ahead of print].

Results from recent studies have supported the beneficial effect of diet and nutrition on the development of cognitive decline and Alzheimer's disease. Researchers have found that diet not only has a therapeutic effect on cognitive function, but also improves mood, cardiovascular risk, weight loss, and insulin resistance. Although researchers have examined how diet affects a variety of cognitive outcomes, such as memory scores and progression to a diagnosis of mild cognitive impairment or Alzheimer's disease, few have examined how diet affects brain biomarkers of Alzheimer's

Summary Point

- A higher-quality diet was associated with larger hippocampal volumes, a well-established marker of Alzheimer's disease risk.

disease, especially among middle-aged, cognitively intact individuals.

Akbaraly et al examined nutritional quality as a predictor of hippocampal volume, a well-established marker of Alzheimer's disease risk, in a prospective cohort of community-dwelling participants from the Whitehall II study, which was designed to investigate long-term health outcomes, particularly cardiovascular disease prevalence and mortality rates, among 10,308 British civil servants recruited from 1985 to 1988.¹ Participants were 35 to 55 years of age at the beginning of the study. Two-thirds were men and one-third women.

Akbaraly et al focused on a subset of 459 participants who received serial dietary exams and a magnetic resonance imaging (MRI) scan of the brain an average of 11 years after the study began. Investigators asked participants to use food frequency questionnaires to track their food patterns over the previous 11 years, and conducted examinations approximately every five years. MRI scans were performed once, in 2015-2016. At the time, participants were an average of 60 years of age and 19% were female.

The food frequency questionnaires measured intake of 11 components (foods and nutrients), including six components for which high intakes are considered ideal (vegetables, fruit, whole grains, nuts and legumes, long-chain omega-3 fats, and total polyunsaturated fatty acids) and five components for which avoidance or low intake is considered ideal (sugar, sweetened drinks and fruit juice, red and processed meat, trans-fat, and sodium).

Based on the intake of these foods and nutrients, the researchers calculated Alternative Healthy Eating Index 2010 (AHEI) scores for each participant at each visit.² A higher score was associated with a higher-quality nutritional diet. Based on AHEI scores, participants were divided into those who maintained a healthy diet, those who maintained a poor-quality diet, those who improved the quality of their diets, and those whose diets got worse over time.

After adjusting for age, sex, and total calorie intake, higher AHEI scores were significantly associated with larger hippocampal volumes. Each one-point increment in AHEI scores was associated with an increase in hippocampal volume by up to 92.5 cc. This effect was independent of a variety of possible confounding factors, such as occupational grade, physical activity, smoking habits, presence of cardiometabolic disorders, cognitive impairment, and depressive symptoms. Participants who maintained a healthy diet or

improved their diet throughout the course of the study had larger hippocampal volumes compared to those who ate a poor-quality diet.

■ COMMENTARY

These findings are consistent with previous work showing that short-term diet quality is associated with preserved brain biomarkers of Alzheimer's disease in middle-aged and older adults.^{3,4} To further support these associations, the authors of two randomized, controlled trials found additional data to support the importance of nutrition for preventing Alzheimer's disease.

[Participants who maintained a healthy diet or improved their diet throughout the course of the study had larger hippocampal volumes compared to those who ate a poor-quality diet.]

In the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability study, researchers found that a lifestyle intervention including nutrition, exercise, and cognitive training reduced the risk of cognitive decline.⁵ In the second trial, researchers found that following a Mediterranean-style diet enriched with extra virgin olive oil or a handful of nuts each day improved memory, attention, and executive function compared to a low-fat diet.⁶ Although additional randomized, controlled trials are needed, recommending targeted dietary interventions in midlife is evidence-based and safe for reducing the risk of cognitive decline and Alzheimer's dementia. ■

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SHORT REPORT

Alcohol Use: No Safe Level

By *Ellen Feldman, MD*

Altru Health System, Grand Forks, ND

Dr. Feldman reports no financial relationships relevant to this field of study.

SYNOPSIS: A systematic analysis of data from the Global Burden of Disease Study 2016 on alcohol-linked disorders and patterns of alcohol use over 25 years worldwide found there is no safe level of alcohol consumption.

SOURCE: GBD 2016 Alcohol Collaborators. Alcohol use and burden for 195 countries and territories, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2018;392:1015-1035.

Do the health benefits of alcohol balance or override the health risks of alcohol consumption? This and related questions spurred an innovative and comprehensive approach to analyzing data obtained from the Global Burden of Diseases, Injuries and Risk Factors Study (GBD) 1990-2016. Collaborators analyzed findings obtained from 195 countries and territories over this 26-year time span and used a variety of newer epidemiological approaches to understand the prevalence of alcohol use, the health risks associated with alcohol use (including disability and development of alcohol-related diseases and death), and any health benefits associated with alcohol use.

The findings are sobering. Among the worldwide population ages 15-49 years, alcohol was the No. 1 cause of disability-adjusted life years (DALY) and the leading risk factor for death, accounting for nearly 10% of deaths in this age group. Among all age groups in 2016, 2.8 million deaths worldwide were linked to alcohol use. When looking at death and DALY among all age groups globally, alcohol rose to the top as the seventh-leading risk factor.

Although alcohol consumption rates vary with geographical boundaries, in 2016, more than 2 billion people worldwide consumed alcohol; about 63% were male. Kuwait, Iran, and Palestine emerged with the lowest death rates related to alcohol use among persons 18-49 years of age (0.3-0.4 % per 100,000 people), while Lesotho, Russia, and the Central African Republic reported the highest death rates attributable to alcohol in this age group (108.8-145.3 per 100,000 people.)

Cardiovascular disease, specific cancers, communicable diseases such as tuberculosis, intentional

Summary Points

- In a review of data from 195 countries over 26 years, researchers found that the level of alcohol consumption minimizing risk is zero.
- Essentially, they found there is no safe level of alcohol intake.

and unintentional injuries, as well as transportation-related injuries were among the 23 disorders and health states associated with alcohol use.

The study authors looked carefully at health benefits associated with alcohol, including investigating evidence linking alcohol consumption to protection from ischemic heart disease and diabetes in women.^{1,2} With a newer approach to the available data, the collaborators concluded that even low levels of alcohol consumption increase the risk of specific cancers in women and that potential health benefits likely are offset by this association. According to the data analysis, the level of consumption minimizing health risk is zero.

Notably, the researchers did not distinguish between types of alcohol consumed or relative content of drinks consumed (percent alcohol was not noted.) Perhaps doing so would have allowed more meaningful results, but at this point there are no data to support or refute this possibility. Arguably, the most meaningful critique of this study is that it was strictly observational; results must be interpreted with due respect to the methodology.

The authors, who were from more than 40 countries, made a case for revising health

guidelines. The study collaborators noted that the current recommendation to consume one to two drinks daily for health benefits is no longer valid and should be revised to reflect “the safest level of drinking is none.” They added that policies addressing alcohol consumption at the population level (such as taxation of alcohol products and cultural modifications) will be most effective at combating the associated health risk.

In a related development, the National Institutes of Health’s Moderate Alcohol and Cardiovascular Health trial — a study about the health benefits of moderate alcohol consumption — was terminated this summer, in part because of methodological concerns that the study design failed to address the potential health risks of moderate alcohol consumption.³

What is the take-home message for our patients? While advocating abstinence from alcohol may seem unrealistic and excessive, it is clearly within

our purview and responsibility to stop promoting drinking for health benefits. This does not mean that we should counsel all patients to stop drinking, but we should be clear that health benefits from alcohol consumption may be overstated and outweighed by risks. Everyday lifestyle and behavior is an essential part of a wellness plan. Providing patients with accurate information about the findings of this study allows each individual to develop a nuanced and comprehensive approach to healthy living. ■

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MENTAL HEALTH

SHORT REPORT

Caregivers and Mindfulness-Based Stress Reduction Interventions

By Ellen Feldman, MD

Altru Health System, Grand Forks, ND

Dr. Feldman reports no financial relationships relevant to this field of study.

SYNOPSIS: A Cochrane Review regarding efficacy of mindfulness-based stress reduction (MBSR) for family caregivers of dementia patients found low-quality evidence that MBSR reduces short-term anxiety and depressive symptoms in this population.

SOURCE: Liu Z, Sun YY, Zhong BL. Mindfulness-based stress reduction for family carers of people with dementia. *Cochrane Database Syst Rev* 2018;8:CD012791.

“With Alzheimer’s disease, it is not just those with the disease who suffer. It’s also their caregivers — a job that usually falls on family and friends.” Alzheimer’s Association¹

Because of the highly stressful nature of caring for a family member with dementia and the association of such caregiving with physical disorders, psychological morbidity, and even early mortality, family caregivers of dementia patients also are known as “the invisible second patient.”² In 2017, 16.1 million family and friends in the United States have held this unpaid role.¹ There have been multiple investigations into various interventions, including mindfulness-based stress reduction (MBSR), to reduce the risk in this population.

Summary Points

- The authors of a review of randomized, controlled trials found that mindfulness-based stress reduction may reduce short-term anxiety and depressive symptoms in people caring for family members with dementia.
- The evidence quality for these trials was low. However, given the low risk of the intervention, it may be a clinical option for this demographic.

Developed by Jon Kabat-Zinn in the late 1970s, MBSR use has grown rapidly and its popularity has increased in subsequent decades. MBSR is a structured program with a range of different practices united by a focus on mindfulness or “the awareness that emerges through paying attention on purpose ... non-judgmentally” Techniques include meditation, yoga, and mindful movement.³

Studies of MBSR in family caregivers of dementia patients have begun to increase in number, but neither a quality meta-analysis nor a systematic review of these studies had been completed. Cochrane Reviews are systematic, evidence-based, commercial-free studies that provide current synthesized information to clinicians, patients, and policymakers.⁴

Liu et al conducted this Cochrane Review to evaluate the effectiveness in use of MBSR for family caregivers of dementia patients. They performed a comprehensive database search for quality studies investigating use of MBSR in family caregivers of dementia patients and identified five trials suitable for inclusion in this meta-analysis. The five trials, which included a total of 201 caregivers, had a high risk for bias because of the difficulty of blinding the subjects and investigators. Three of the trials included active control groups, such as progressive muscle relaxation, and two of the trials included inactive control arms, such as respite

care. Given these and other factors, the Cochrane rating of the evidence in general is of low quality. See Table 1 for a summary of results.

When compared with active control after eight weeks of intervention, there was low-quality evidence that MBSR reduces symptoms of anxiety and depression in family caregivers of dementia patients. On the other hand, when MBSR was compared to inactive controls over this same period, there was no evidence of an effect on depressive symptoms and very limited evidence regarding an effect on anxiety. Since the quality of the evidence was low, it is not possible to draw firm conclusions. Three trials with a total of 135 participants suggested that caregivers who received MBSR vs. active control may have reported more incidents of feeling burdened. No determination could be drawn for this category for MBSR vs. inactive control because of the very low-quality evidence.

High-quality research is needed to determine how, and even if, MBSR is effective in alleviating stress for family caregivers of dementia patients. However, while waiting for such results, there is little risk in offering the results of this review as preliminary guidelines for caregiver self-care.

For now, a useful take-home message for clinicians is to be mindful of the importance of addressing “the invisible patient” in the office when

Table 1: Summary of Results on Mindfulness-Based Stress Reduction for Dementia Caregivers

	Number of trials and participants	Standardized mean difference (95% confidence interval)	P value	Evidence quality
MSBR vs. active control: depressive symptoms	3 trials; 135 participants	-0.63 (-0.98 to -0.28)	<i>P</i> < 0.001	Low quality
MSBR vs. active control: anxiety symptoms	1 trial; 78 participants	-7.50 (-13.11 to 1.89)	<i>P</i> < 0.001	Low quality
MSBR vs. active control: perception of burden	3 trials; 135 participants	0.24 (-0.11 to 0.58)	<i>P</i> = 0.18	Low quality
MSBR vs. inactive control: depressive symptoms	2 trials; 50 participants	-1.97 (-6.89 to 2.95)	<i>P</i> = 0.43	Low quality
MSBR vs. inactive control: anxiety symptoms	1 trial; 33 participants	-7.27 (14.92 to 0.38)	<i>P</i> = 0.06	Low quality
Bold = important findings				

caring for patients with dementia. Educating caregivers regarding this and other similar studies may be helpful in validating caregiver feelings and provide a springboard to further discussion and possible intervention. ■

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PROBIOTICS

SHORT REPORT

Probiotic Use to Reduce *Clostridium difficile*-Associated Diarrhea

By *Nadia Khosrodad, MD; Justin Khine, MD; and Nancy J. Selfridge, MD*

Dr. Khine is a Clinical Teaching Fellow in the Department of Clinical Medicine at Ross University School of Medicine, Bridgetown, Barbados, West Indies.

Dr. Khosrodad is a PGY1 Internal Medicine Resident at St. Joseph Mercy Oakland Hospital, Pontiac, MI.

Dr. Selfridge is Chair of the Department of Clinical Foundations, Ross University School of Medicine, Bridgetown, Barbados, West Indies.

Dr. Khine, Dr. Khosrodad, and Dr. Selfridge report no financial relationships relevant to this field of study

SYNOPSIS: In a systematic review of probiotic use for reducing *Clostridium difficile*-associated diarrhea (CDAD), probiotics appear to be most beneficial in populations with high baseline risk of CDAD (> 5%).

SOURCE: Goldenberg JZ, Yap C, Lytvyn L, et al. Probiotics for the prevention of *Clostridium difficile*-associated diarrhea in adults and children (review). *Cochrane Database Syst Rev* 2017;12:CD006095.

A causal link between gut microflora perturbation by antibiotics and *Clostridium difficile*-associated diarrhea (CDAD) has long been established. However, therapeutic or prophylactic use of probiotics for CDAD has been viewed skeptically because of inconsistent reports of treatment efficacy. *C. difficile* infection (CDI) is an expensive disease with total annual attributable costs estimated at \$6.3 billion and total annual inpatient management days estimated at 2.4 million in the United States.¹ Effective prophylactic therapy potentially could decrease hospital length of stay, mitigate associated complications and patient suffering, and reduce the financial burden of CDI significantly.

In this meta-analysis, Goldenberg et al identified 39 clinical trials that met inclusion criteria for assessing probiotic efficacy in reducing a primary outcome of incidence of CDAD or antibiotic-associated diarrhea. They chose 31 trials assessing CDAD outcomes for data collation and analyses, which included probiotic dose, species/strains, adult vs. pediatric patients, inpatients vs. outpa-

Summary Point

- In this Cochrane Review of 31 studies, probiotic treatment appears to confer up to 70% risk reduction for *Clostridium difficile*-associated diarrhea in high-risk patients without associated adverse effects and with an apparent reduction in adverse events compared to either placebo or no treatment.

tients, risk of bias, and baseline risk of CDAD. The quality of evidence was assessed independently using the GRADE criteria.²

Twenty-two of the 31 studies had missing data for the outcome ranging from 2-45%. Thus, the authors performed a complete case analysis for the 8,672 participants who completed the study. The risk of CDAD in this group was 1.5% in the probiotic treatment group compared to 4% in the placebo or no treatment control group (relative

risk [RR], 0.40; 95% confidence interval [CI], 0.30-0.53), an estimated 60% risk reduction in the treatment group. In a post-hoc analysis, the authors noted one large study comprising nearly 2,810 participants and several other smaller studies that failed to find a statistically significant effect of probiotics on reducing CDAD outcomes. They determined that the baseline risk of CDAD in these study populations was very low (< 5%). The overall risk reduction estimate of probiotic therapy in this analysis is heavily influenced by a number of studies with high baseline risk, including five trials showing a CDAD baseline risk > 15%. Thus, the protective effect of probiotics may not be applicable to low-risk populations. An increased baseline risk of CDAD is widely accepted as associated with advanced age, severity of comorbidities, prolonged hospitalization, and antibiotic use. Antibiotic exposure further stratifies the risk depending on the antibiotic used: High risk is associated with second- and third-generation cephalosporins, fluoroquinolones, and clindamycin; moderate risk with amoxicillin-clavulanic acid and macrolides; and low risk with all others.³

The authors found no association in subgroup analyses to determine if probiotic species, strain, or dose influenced CDAD outcome. Many of the included trials demonstrated high or indeterminate risk of bias, and many had other significant methodological flaws reducing the quality of

evidence, which was reported as moderate for the primary outcome according to GRADE criteria. There were no attributable adverse effects associated with probiotics, and overall adverse events were lower in the probiotic group vs. control groups. The risk reduction effect of probiotics on adverse events was estimated at 17% (RR, 0.83; 95% CI, 0.71-0.97), although the quality of evidence (GRADE) for this effect was very low, primarily because of nonstandardized, clear event reporting across studies. Further, results of these trials cannot be generalized to immunocompromised patients.

Despite the need for additional high-quality research to confirm certainty of evidence and provide more detailed information concerning dosing and strains, informing immune-competent patients at high risk for CDAD of the large protective effect of probiotic therapy and encouraging probiotic prophylaxis is sound patient-centered care based on the results of this meta-analysis. ■

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ELDERLY

SHORT REPORT

The Mediterranean Diet and Cognitive Function: Keep the Mind Sharp

By Joseph E. Scherger, MD, MPH

Core Faculty, Eisenhower Health Family Medicine Residency Program, Eisenhower Health Center, La Quinta, CA; Clinical Professor, Keck School of Medicine, University of Southern California, Los Angeles

Dr. Scherger reports no financial relationships relevant to this field of study.

SYNOPSIS: Italian seniors who ate a high-quality Mediterranean diet had better cognitive function than those who did not.

SOURCE: De Amicis R, Leone A, Fippiani A, et al. Mediterranean diet and cognitive status in free-living elderly: A cross-sectional study in Northern Italy. *J Am Coll Nutr* 2018;37:494-500.

A group of Italian investigators from Milan, Pavia, and Brescia, Italy, performed a cross-sectional study that included 279 seniors 65 years of age and older to study the subjects' diet and cognitive function. The Mediterranean diet was assessed using a 14-item questionnaire. Cognitive function was assessed with the Mini-Mental State

Examination. They found that 30.1% of subjects met the criteria for a healthy Mediterranean diet and 13.6% had suspected or mild cognitive decline. Adherence to the Mediterranean diet was associated with a lower risk of cognitive impairment (odds ratio [OR], 0.39). This effect also was seen when subjects consumed more than three

Summary Point

- High adherence to the Mediterranean diet in 279 adults in Italy aged 65 or older correlated with a lower risk of cognitive impairment as per the Mini-Mental Status Examination.

glasses of wine per week (OR, 0.37). Researchers did not observe any association for other food groups.

These findings are consistent with other research that found adherence to a Mediterranean diet may lead to better cognitive function.¹⁻³ However, what constitutes a proper and healthy Mediterranean diet is confusing and may mean different things to physicians and the public. The 14 items from the Mediterranean diet questionnaire include:

- Using olive oil as the primary cooking fat;
- More than four tablespoons of olive oil daily;
- More than two servings of vegetables daily;
- Three or more daily servings of fruit;
- Less than one daily serving of red or processed meat;
- Less than one daily serving of butter, cream, or margarine;
- Less than one sugar-sweetened beverage per day;
- Three or more glasses of wine per week;
- Three or more servings of legumes per week;
- Three or more servings of fish/seafood per week;
- Fewer than three commercial and confectionary sweets per week;

- One or more servings of nuts per week;
- More white meat than red meat;
- Using soffritto, a mixture of slowly cooked carrots, onions, and celery that is used as a base to add flavor to sauces, soups, and stews. (Sometimes, carrots, onions, and celery are called the “holy trinity” in Italian cuisine.⁴)

Importantly, pasta is not mentioned as part of a healthy Mediterranean diet. With its emphasis on olive oil, vegetables (including avocado), nuts, and seafood, the Mediterranean diet includes healthy fats and protein as its main macronutrients and is low carbohydrate. Carbohydrates are obtained only from whole foods such as fruit. A healthy Mediterranean diet has stood the test of time as possibly the healthiest way to eat.^{5,6} It should be standard medical advice for anyone not adhering to a whole food, plant-based diet. ■

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CME QUESTIONS

- Which of the following statements regarding vitamin D supplementation is false?**
 - Vitamin D supplements have been found to contain higher amounts of vitamin D than the label claims.
 - Vitamin D use in the United States has decreased since 1999.
 - Serum 25(OH)D levels at ≥ 150 ng/mL are associated with toxicity.
 - Serum 25(OH)D levels are not indicative of body storage of vitamin D.
- Which of the following food categories is not part of a high-quality diet?**
 - Fresh fruits and vegetables
 - Nuts and legumes
 - Sweet fruit juices
 - Whole grains
- Which of the following statements is true about the recommendations from the GBD Alcohol Collaborators?**
 - Findings were biased because of difficulty obtaining and comparing information from multiple organizations and diverse geographical locations. All recommendations should be reviewed with this in mind.
 - This review clearly pointed out the risks of alcohol use, but fails to examine the health benefits closely.
 - This review incorporated data regarding both the risks and health benefits of alcohol use and concluded that public health guidelines should reduce recommendations regarding alcohol use to reflect that the level of alcohol use to minimize health benefits is zero.
 - This review incorporated data regarding both the risks and health benefits of alcohol use and concluded that public health guidelines should reduce recommendations to one to two drinks weekly rather than daily.
- Which of the following statements is true regarding mindfulness-based stress reduction (MBSR) based on results of a recent Cochrane Review?**
 - There was moderate-quality evidence showing that MBSR alleviates symptoms of depression in caregivers of dementia patients and higher-quality evidence showing MBSR alleviates anxiety in the caregivers at six months to one year follow-up.
 - There was low-quality evidence showing MBSR alleviates symptoms of depression and anxiety in family caregivers of dementia patients at the end of an eight-week treatment period compared to active controls.
 - There was low-quality evidence showing that MBSR alleviates symptoms of depression and moderate-quality evidence in clinical relief of depression in family caregivers of dementia patients at the end of an eight-week treatment period compared to inactive controls.
 - There was low-quality evidence showing MBSR alleviates perception of burden in family caregivers of dementia patients at the end of an eight-week treatment period compared to active and inactive controls.
- Which of the following is not part of a healthy Mediterranean diet?**
 - At least 4 tablespoons of olive oil per day
 - Up to two servings of pasta per week
 - Up to three glasses of wine per week
 - At least three servings of fish per week

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- present evidence-based clinical analyses of commonly used alternative therapies;
- make informed, evidence-based recommendations to clinicians about whether to consider using such therapies in practice; and
- describe and critique the objectives, methods, results, and conclusions of useful, current, peer-reviewed, clinical studies in alternative medicine as published in the scientific literature.

[IN FUTURE ISSUES]

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