

# Integrative Medicine

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

## OBESITY

### ABSTRACT & COMMENTARY

# Olive Oil or Mixed Nuts Consumption, as Part of the Mediterranean Diet, May Help Reduce Body Weight and Central Adiposity

By David Kiefer, MD, Editor

**SYNOPSIS:** The long-term vegetable fat enrichment of a Mediterranean diet leads to less weight gain and less increase of central adiposity than a control diet.

**SOURCE:** Estruch R, Martinez-Gonzalez MA, Corella D, et al. Effect of a high-fat Mediterranean diet on bodyweight and waist circumference: A prespecified secondary outcomes analysis of the PREDIMED randomised controlled trial. *Lancet Diabetes Endocrinol* 2016; Jun 6. pii: S2213-8587(16)30085-7. doi: 10.1016/S2213-8587(16)30085-7.

**T**his study is another reworking of the large PREDIMED trial that brought us information about the benefits of the Mediterranean diet on numerous conditions, including cardiovascular disease, breast cancer, and Alzheimer's disease. PREDIMED, or PREvención con DIeta MEDiterránea, is a five-year, multicenter, randomized, controlled trial that includes 7,447 people at high cardiovascular risk (type 2 diabetes or three or more cardiac risk factors). It has three arms: 1) a Mediterranean diet with no calorie restriction and enriched with extra-virgin olive oil (EVOO) (n = 2,543); 2) a

Mediterranean diet with no calorie restriction and enriched with mixed nuts (n = 2,454); or 3) a control diet (participants were advised to avoid all dietary fat; n = 2,450). The primary outcome was the primary prevention of cardiovascular disease (this was proven and received widespread media attention). However, the secondary outcome of interest in the article being reviewed here was the effect of these different diets on body weight and waist circumference.

After randomization, study participants met with trained dietitians approximately every three

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## Summary Points

- This was a randomized, controlled trial investigating the effects of Mediterranean diet enriched with either extra-virgin olive oil or mixed nuts on body weight and central adiposity over five years in people with cardiovascular disease risk.
- The olive oil group lost 0.43 kg more weight ( $P = 0.44$ ), and gained 0.56 cm less waist circumference ( $P = 0.48$ ) than those eating a control diet.
- The mixed nuts group gained almost a full centimeter less (0.94 cm;  $P = 0.006$ ) of waist circumference than the control group.
- There are many possible physiological reasons for the effects seen, including the antioxidant (polyphenol) content of olive oil and the benefits of dietary fat vs. carbohydrate.

months to receive individualized dietary advice about the Mediterranean diet (two intervention arms) or about how to limit all dietary fat (the control diet). The goal was to reduce fat to less than 30% of calories (control diet) or increase fat to more than 40% of calories (two intervention arms). The two intervention arms were supplemented, free of cost, with one liter of EVOO weekly or 30 grams of mixed nuts daily. At baseline and annually for five years, trained personnel measured waist circumference to 0.5 cm and body weight on calibrated scales to 0.5 kg. Diet questionnaires closely followed adherence to the different dietary arms.

The median time of follow-up was 4.8 years. At the end of the trial, 1,501 participants in the EVOO group, 1,241 participants in the mixed nuts group, and 1,243 participants in the control group remained in the trial and were assessed. The authors accounted for all study dropouts, and analyzed the data in an intention-to-treat analysis.

The mean age of the study participants was 67 years, 40-46% were male, the range in body weight was 76.6-77.0 kg, and the range of waist circumference was 100.2-100.9 cm, depending on the group. More than 90% of the participants were overweight or obese. Over the five years, predictably, the EVOO group had an increase in consumption of EVOO (and, interestingly, mixed nuts) and the

mixed nuts group showed an increase in mixed nuts consumption — no surprise there. Both Mediterranean diet groups ingested more vegetables, legumes, fruits, and fish, and ate fewer sweets, meat, and dairy. After five years, the control group went from an average of 40.0% of calories from fat to 37.4% ( $P < 0.001$ ), whereas the EVOO and mixed nuts groups increased fat calorie percentage from 40.0% to 41.8% and 40.4% to 42.2%, respectively ( $P < 0.001$ ).

With respect to the outcomes, all three groups had a slight decrease in body weight and a slight increase in waist circumference (see Table 1). However, when compared to the control diet, the two intervention diets showed some interesting trends (see Table 2). For example, the participants eating a Mediterranean diet with EVOO lost 0.43 kg more weight ( $P = 0.44$ ), and gained 0.56 cm less waist circumference ( $P = 0.48$ ) than those eating a control diet. The mixed nuts group had a similar ( $P = 0.73$ ) loss of body weight as the control group, but gained almost a full centimeter less (0.94 cm;  $P = 0.006$ ) of waist circumference than the control group.

#### ■ COMMENTARY

There are several important takeaways from this study. First is that, as we all know, it is difficult, but not impossible, to change one's diet. In all three arms, participants were able to shift the percentage of their calories from fat,

**Table 1: Changes in Body Weight and Waist Circumference in Three Diets after Five Years**

	Body Weight	Waist Circumference
Control diet	-0.6 kg	+1.2 cm
Mediterranean diet with extra-virgin olive oil	-0.9 kg	+0.8 cm
Mediterranean diet with mixed nuts	-0.4 kg	+0.4 cm

**Table 2: Difference in Body Weight and Waist Circumference in Two Intervention Diet Arms When Compared to Control Diet**

	Body Weight	Waist Circumference
Mediterranean diet with extra-virgin olive oil	-0.43 kg ( $P = 0.44$ )	-0.55 cm ( $P = 0.048$ )
Mediterranean diet with mixed nuts	-0.08 kg ( $P = 0.73$ )	-0.94 cm ( $P = 0.006$ )

albeit slightly. It could be argued that this small adjustment to nutrition required, or at least benefitted from, regular meetings with dietitians and the provision of supplemental EVOO or mixed nuts. Could we achieve such results in our patient population? Yes, but we might need to brainstorm with our clinic staff to determine the best way to regularly counsel and support our patients on their road to nutrition and lifestyle change.

Second, changing one's diet does indeed affect physiology. In this case, perhaps the changes are not striking, but they are there. In the Mediterranean diet groups, the participants were able to halt their midsection growth, and even lose a bit more weight than the control group. There likely are complicated physiological factors at work, given what the scientific community is starting to learn about nutritional (especially carbohydrate) connections to and diabetes risk with central obesity, but at least we can say that this five-year intervention did have an effect. It will have to be left to future studies to determine the how and why. Related to this is the fact that the authors claimed to rebuke the hypothesis that high vegetable-fat diets, such as the two intervention arms here, will promote weight gain and central adiposity. Such concerns were mostly seen in the low-fat dietary push a few decades ago, but nonetheless are still seen in some current clinical recommendations. The growing body of evidence now speaks to the fact that we shouldn't be afraid of fat, especially EVOO or those from a moderate amount of mixed nuts.

Another interesting conclusion from this study is

that some of the results were more pronounced in the EVOO group than the mixed nuts group. Why might that be the case? EVOO contains more than just the important monounsaturated fat, oleic acid. The "catch" in the back of the throat that comes from eating high-quality EVOO is due to a family of antioxidant compounds, polyphenols, which may give an extra positive boost to the physiologic effects seen in this study.

As clinicians try to translate these results into clinical practice, it is important to keep in mind the demographic studied here: older overweight individuals at risk for cardiovascular disease, the majority of whom were women. In these cases, there should be no fear of increasing fat intake from EVOO or mixed nuts; the benefits on body weight and waist circumference may be small, but they are significant. ■

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## ABSTRACT &amp; COMMENTARY

# Individualized Integrative Medicine Treatment for Preoperative Anxiety

By *Ellen Feldman, MD*

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

SOURCE: Attias S, Keinan B. Effectiveness of integrating individualized and generic complementary medicine treatments with standard care versus standard care alone for reducing preoperative anxiety. *J Clin Anesth* 2016;29:54-64.

SYNOPSIS: In a randomized, clinical trial investigating the treatment of preoperative anxiety, standard sedating medication with a specified add-on individualized integrative technique is the most effective intervention.

Anxiety prior to surgery is common and can be a significant factor in postoperative morbidity and mortality.<sup>1</sup> Multiple studies demonstrate that preoperative anxiety may negatively affect the course of surgery and the postoperative period (via increased use of anxiolytics and/or via direct physiological changes, including increases in blood pressure and pulse), but there are few controlled studies regarding reducing anxiety in this setting. Attias et al conducted a randomized, controlled trial investigating the relative effect of specific treatments on preoperative anxiety. Each arm of the study includes conventional or standard anxiolytic medication (ST) with or without a specified add-on integrative medicine treatment (IMT).

The aim of the investigation is to examine reduction of preoperative anxiety with ST alone compared with ST plus a generic IMT or ST plus an individualized IMT.

Conducted over a period of three years, Israeli researchers recruited patients on a general surgical ward. Out of 519 patients eligible for participation, 360 completed the investigation, including both baseline and post-intervention assessment of anxiety.

Randomization was accomplished by assigning patients to groups via sealed envelopes. Patients were assigned to either ST alone (premedication with a benzodiazepine); ST plus a commercially available compact disc recording of guided imagery recording (CDRGI); or ST plus one of the following individualized treatments randomized according to the day of the week: individualized acupuncture, reflexology, guided imagery or

## Summary Points

- This study randomized 360 preoperative patients into six groups to receive: 1) standard anxiolytic treatment (ST), 2) ST plus a compact disk recording of guided imagery (CDRGI), 3) ST plus acupuncture, 4) ST plus individualized guided imagery, 5) ST plus reflexology, or 6) ST plus reflexology plus individualized guided imagery.
- The group receiving ST alone showed no significant difference in measurement of level of anxiety pre- or post-treatment.
- All groups receiving add-on integrative interventions showed a statistically significant reduction in preoperative anxiety; the groups receiving ST plus individualized interventions showed statistically significant greater reduction in anxiety than the group receiving ST plus CDRGI.
- When looking at the four groups receiving an individualized treatment (plus ST), there is no statistical evidence pointing to superiority of any one treatment in reduction of preoperative anxiety.

reflexology plus guided imagery, specific to the patient as per below. Each group completed the study with 60 patients.

Acupuncture treatment was individualized in accordance with the traditional Chinese medicine

diagnoses. Reflexology points were selected “according to the patients’ mental and physical condition.” Guided imagery was specific to the surgical procedure. Anxiety was measured using a validated anxiety questionnaire, a Visual Analog Scale (VAS), with possible scores between 0 (no anxiety) and 10 (maximum anxiety). Participants were asked to complete the scale twice: once after entering the study and then again after intervention, but before surgery. Thus, both measurements were taken preoperatively within a 30-60 minute period. It is worth noting again that every patient received ST; dose and type of medication was left to the judgment of the anesthesiologist (either PO oxazepam 10 mg or diazepam 5-10 mg.)

Baseline scores of anxiety were elevated, with more than 70% of participants in all groups scoring higher than 4 (3 is generally the cutoff for moderate anxiety.)

Figure 1 shows anxiety scores pre- and post-intervention when comparing all groups receiving IMT + ST (n = 300) with ST alone (n = 60.) The consolidated group of 300 patients included the group receiving generic IMT (CDRGI) plus ST, as well as the four groups receiving individualized IMT plus ST.

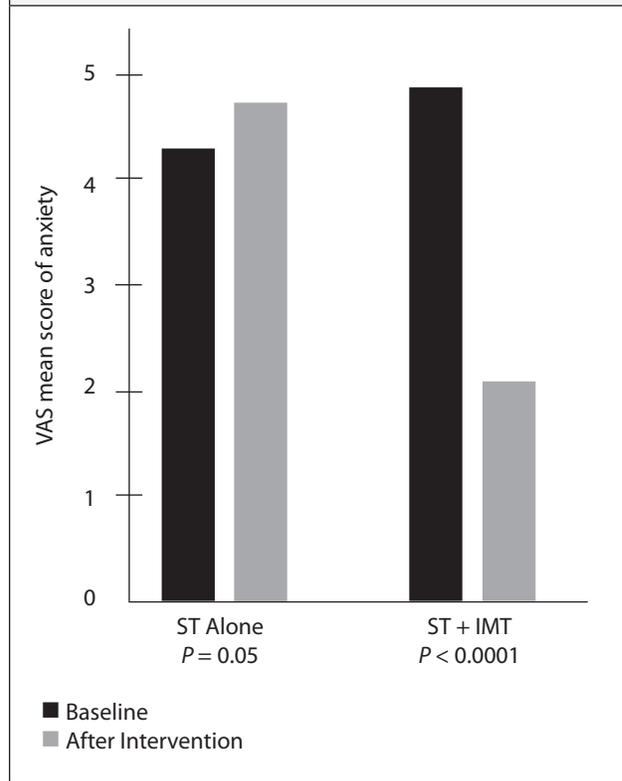
All anxiety scores dropped post-intervention in the groups receiving IMT and ST, demonstrating a reduction of anxiety, although to different degrees (see Figure 2). The group receiving ST alone showed a mean increase in anxiety scores; this increase was not shown to be statistically significant.

Figure 2 compares results from each group receiving any form of IMT (in combination with ST.) Statistical analysis (as explained by the authors) shows no significant difference in results when comparing the individualized IMT head-to-head. However, there was a statistically significant effect ( $P < 0.0001$  for each) when comparing each individualized treatment to CDRGI.

#### ■ COMMENTARY

Why all the *worry* about preoperative anxiety? Although there has been some historical thought that preoperative anxiety actually may be protective in the postoperative period,<sup>2</sup> recent studies have found that high levels of preoperative anxiety are not desirable.<sup>1,3,4</sup> These studies noted that preoperative anxiety levels correlate with longer hospital stays, adverse perioperative outcomes, and poorer patient satisfaction scores.<sup>3,4</sup>

**Figure 1: ST Alone vs. ST + IMT: Preoperative Anxiety**



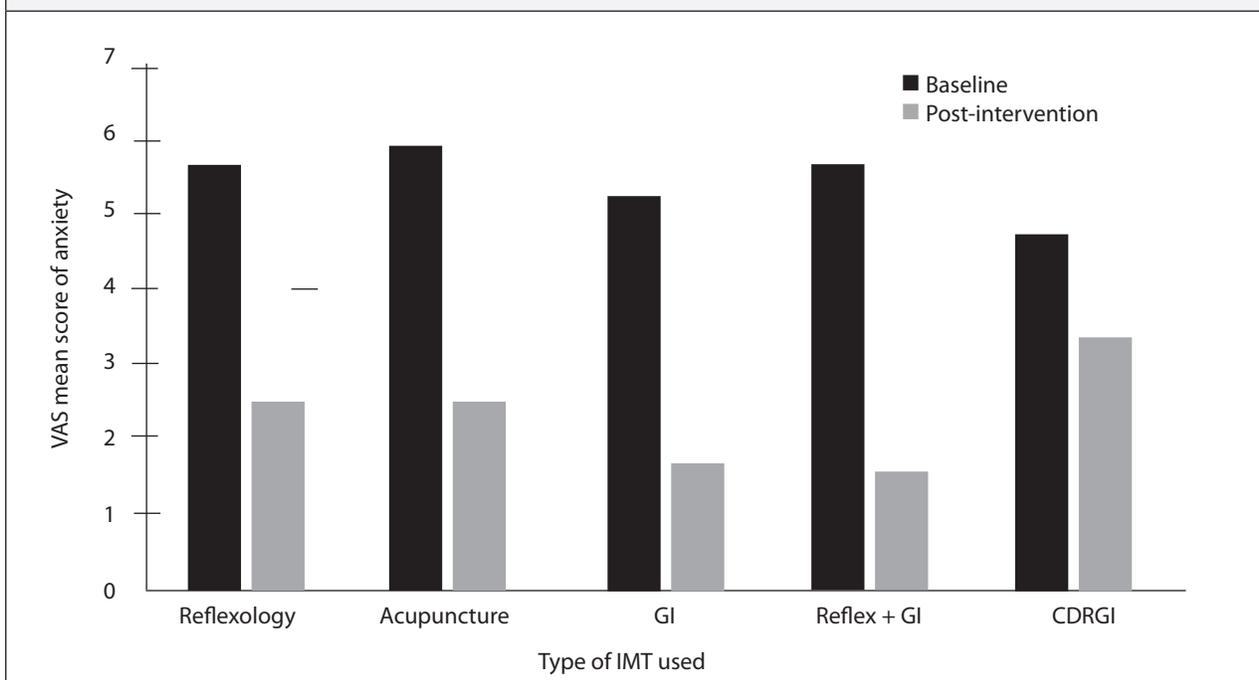
Increased use of anxiolytic medication may lead to secondary problems such as excessive sedation, confusion, and interactions with anesthesia.<sup>5</sup> Investigations looking at cardiovascular procedures have linked preoperative anxiety with increased mortality.<sup>6</sup> Given the risks, many interventions to reduce anxiety in the preoperative period actively are being explored.

Preoperative education<sup>7</sup> and music,<sup>8</sup> as well as the interventions used in this study, all have been studied as alternatives or add-ons to conventional anxiolytic medication in a preoperative setting. All seem to have potential use in this arena, although well-controlled and well-designed studies are still needed.

However, there are few studies that look at the manner of administration of an integrative medical technique to determine if the modality itself affects outcome. There are few studies that look at relative efficacy of integrative techniques.<sup>1</sup> These are the unique factors incorporated into the design and purpose of this investigation.

This study looked at adding IMT to a conventional benzodiazepine regimen and then, even more specifically, at the manner of administration of IMT — generic (in this case prerecorded on a

**Figure 2: Effect on Mean Anxiety Scores: IMT + ST**



CD) vs. customized. There is a mention that the relatively more robust effect of the individualized treatments may be due to the “human factor” — future studies looking at individualized treatments without hands-on involvement could be helpful in sorting this out.

Another aspect of the IMTs chosen for this study is that each has been studied in treatment of anxiety disorders.<sup>8,9</sup> However, it is important to differentiate between a disorder of anxiety and an anxious mood or state occurring in the context of impending surgery. This study strictly looked into treatment of an anxious state (known as “state anxiety”) measured by self-assessment on a validated scale; there are no claims or implications for the treatment of anxiety disorder on the basis of this work. In this case, validation means that a measurement on the VAS correlates with other known measurements of state anxiety.<sup>10</sup> Unfortunately, there is very little published information linking changes in physiologic parameters directly with measurements of state anxiety.

This may explain why the benzodiazepines used as ST in the study failed to show an effect on levels of anxiety. Previous studies have demonstrated moderate effectiveness of these agents in treatment of preoperative anxiety,<sup>11</sup> so it is puzzling why they showed no effect here. It may be a factor of timing (determined by when the second measurement of anxiety was taken), but also may

have to do with the subjective nature of the scale used to measure anxiety and the absence of any objective determinants of relief of anxiety. That is, there is no information from this study regarding objective measurements of any parameters related to an anxious state and so no way to know if measurements in addition to the VAS would have reflected an effect of these agents or been more sensitive to distinguishing effects from the various IMTs.

Relevant literature fails to fully explain if the perioperative risks related to preoperative anxiety are due to self-awareness of anxiety or expected physiological changes due to state anxiety, or a combination of the two factors. This is another area ripe for future exploration.

The authors made clear that theirs is an exploratory study and that there were no investigations into any positive or negative implications of the IMTs after the second measure of anxiety just prior to surgery. To definitively link IMTs to clinically significant preoperative anxiety relief and to reduction in perioperative complications linked with preoperative anxiety, it will be important for future studies to explore not only subjective measures of anxiety but also some objective measures as well (blood pressure, heart rate, or even length of time in surgery, postoperative complications, hospitalization length, etc.).

There is little doubt (as noted by studies mentioned above) that addressing anxiety in a preoperative setting is helpful in reducing perioperative complications. This study reinforces the idea that IMTs reduce the experience of anxious feelings during the preoperative period, and introduces the concept that the method of administration of the IMT may be as important as the type of IMT used.

Understanding how and why individualizing an IMT leads to increased efficacy will be important in advancing the field of integrative medicine. The relative ease of individualization makes this an area ripe for exploration. Of course, the flip side is that this study and others of a similar design rely heavily on expertise of a particular practitioner. This can add to difficulties identifying direct causal relationships as standardization challenging.

Essential elements in future studies include understanding the relationship between self-reporting an anxious state and exhibiting cardiovascular and other objective measures of this state. Changes in cardiovascular parameters with decline of self-assessed anxiety would be useful to explore as well. With this link clearly established, more definitive conclusions can be drawn.

The medical field appears to be rapidly moving toward adopting many integrative therapies as

mainstream. Understanding specific efficacies and mechanism of action of each intervention will help cement legitimacy and propel this movement forward. Understanding how much individualized therapy contributes to their effect also will be an important consideration. ■

#### REFERENCES

1. Wilson CJ, Mitchelson AJ, Tzeng TH, et al. Caring for the surgically anxious patient: A review of the interventions and a guide to optimizing surgical outcomes. *Am J Surg* 2016;212:151-159.
2. Anxiety before surgery may prove healthful. The Free Library 2014. Available at: <http://www.thefreelibrary.com/Anxiety+before+surgery+may+prove+healthful.-a012291606>. Accessed June 25, 2016.
3. Hobson JA, Slade P, Wrench IJ, Power L. Preoperative anxiety and postoperative satisfaction in women undergoing elective caesarean section. *Int J Obstet Anesth* 2006;15:18-23.
4. Caumo W, Hidalgo MP, Schmidt AP, et al. Effect of pre-operative anxiety on postoperative pain response in patients undergoing total abdominal hysterectomy. *Anaesthesia* 2002;57:740-746.
5. Pan PH, Tonidandel AM, Aschenbrenner CA, et al. Predicting acute pain after cesarean delivery using three simple questions. *Anesthesiology* 2013;118:1170-1179.
6. Székely A, Balog P, Benko E, et al. Anxiety predicts mortality and morbidity after coronary artery and valve surgery — a 4-year follow-up study. *Psychosom Med* 2007;69:625-631.
7. Ayyadhah A. Reducing anxiety in preoperative patients: A systematic review. *Br J Nurs* 2014;23:387-393.
8. Bradt J, Dileo C. Music Interventions for preoperative anxiety. *Cochrane Database Syst Rev* 2013; Jun 6:CD006908.
9. van der Watt G, Laugharne J, Janca A. Complementary and alternative medicine in the treatment of anxiety and depression. *Curr Opin Psychiatry* 2008;21:37-42.
10. Facco E, Zanette G, Favero L, et al. Toward the validation of visual analogue scale for anxiety. *Anesth Prog* 2011;58:8-13.
11. Pekcan M, Celebioglu B, Demir B, et al. The effect of premedication on preoperative anxiety. *Middle East J Anesthesiol* 2005;18:421-433.

## DEMENTIA

### ABSTRACT & COMMENTARY

# Seafood Consumption and Brain Mercury Levels in Older Adults with Dementia

By Traci Pantuso, ND, MS

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

**SYNOPSIS:** This cross-sectional study of older adults who were part of the Rush Memory and Aging Project demonstrated that moderate seafood consumption was correlated with a decreased level of brain Alzheimer's disease neuropathology in APOE ε4 carriers. Higher brain levels of mercury were correlated with higher seafood consumption. However, these levels were not correlated with brain neuropathology.

**SOURCE:** Morris MC, Brockman J, Schneider JA, et al. Association of seafood consumption, brain mercury level, and APOE e4 status with brain neuropathology in older adults. *JAMA* 2016;315:489-497.

Observational studies have demonstrated that increased intake of omega-3 polyunsaturated fatty acids (n-3 PUFA), which are found in seafood

and other foods, have been associated with slowing cognitive decline and a decreased risk of Alzheimer's disease (AD) and dementia in older

## Summary Points

- A higher intake of  $\alpha$ -linolenic acid was correlated with a decreased risk of cerebral infarcts.
- There was no correlation between seafood consumption and neuropathology among those who were APOE  $\epsilon$ 4 negative.
- There were no significant correlations found between fish oil supplementation and any Alzheimer's disease neuropathology.

adults.<sup>1,2</sup> However, seafood consumption also can lead to increased levels of mercury, a known neurotoxin.<sup>1,2</sup> The APOE gene encodes instructions for making apolipoprotein A, which combines with lipids to form lipoproteins. The APOE gene variant APOE  $\epsilon$ 4 is associated with an increased risk of AD.<sup>3</sup> APOE  $\epsilon$ 4 is present in 25-30% of the population and 40% of people with late onset AD.<sup>3</sup> Individuals with the double allele have a 10-fold increased risk of late onset AD.<sup>3</sup>

To further understand the role of dietary seafood intake and brain neuropathology, Morris et al examined 286 brains from deceased older adult participants enrolled in the larger Rush Memory and Aging Project (MAP) study who died between 2004 and 2013. The MAP study is an ongoing study being conducted in Chicago with predominately white, non-Hispanic participants residing in retirement communities and subsidized housing. The adults in the MAP study did not have dementia at the time of enrollment and completed a dietary assessment before death. The autopsied brains were evaluated for AD neuropathology, including both diffuse and neuritic amyloid plaques as well as neurofibrillary tangles. Counts of chronic macroscopic cerebral infarctions and microinfarcts were performed along with Lewy body staging. Brain selenium and mercury metal concentrations were determined by instrumental neutron activation analysis and were measured in the inferior temporal and midfrontal cortical regions and in the cerebellum. Linear regression models (statistical significance,  $P < 0.05$ ) were used to investigate the associations of dietary variables and brain metal concentrations with AD neuropathology.

The participants in this study are representative of 51.6% of all deceased MAP participants. The mean age of death was 89.9 years and 67% were women. The mean educational attainment was

14.6 years, and 22.7% were positive for the APOE  $\epsilon$ 4 allele. In the highest tertile of dietary n-3 PUFA intake, there were more women, and in the lowest tertile of dietary n-3 PUFA intake, there was a higher likelihood of being APOE  $\epsilon$ 4 positive.

To measure dietary consumption of seafood intake, a semiquantitative food frequency questionnaire previously validated for use in older Chicago residents was administered annually starting in 2004. The questionnaire featured four seafood items that were measured to calculate weekly seafood consumption. To calculate daily PUFA intake, eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and  $\alpha$ -linolenic acid amounts were multiplied by the nutrient content of all food items by frequency of consumption and then summed. The questionnaire also asked about fish oil supplements, which were then averaged over all valid food frequency questionnaires obtained before death.

Participants who noted that they used fish oil supplements on one of the food frequency questionnaires were considered to be supplementing with fish oil. Forty-nine participants reported taking fish oil supplements and of these, 31 participants only positively reported supplementation on one visit survey.

APOE  $\epsilon$ 4 individuals who consumed one or more seafood meals per week had decreased AD neuropathology compared to APOE  $\epsilon$ 4 individuals who consumed less than one meal per week. There was no correlation between seafood consumption and neuropathology among those who were APOE  $\epsilon$ 4 negative. There were no significant correlations found between fish oil supplementation and any AD neuropathology for either group.

Increased dietary  $\alpha$ -linolenic acid was found to be correlated with a decreased risk of cerebral microinfarcts ( $P = 0.03$ ) and macroinfarcts ( $P = 0.04$ ), while EPA and DHA did not demonstrate this effect. However, in APOE  $\epsilon$ 4 individuals, there was a correlation between decreased risk of macroinfarcts and fish oil supplementation ( $P$  for interaction = 0.05)

The researchers analyzed 203 cases for brain concentrations of mercury and selenium in the inferior temporal and midfrontal cortical region of the brain, centers of the brain known to be involved in AD, as well as in the cerebellum (less likely to be affected by AD neuropathology). The mean (SD) for brain mercury concentrations in the inferior temporal region was 0.25 (0.78), 0.26

**Table 1: Alzheimer's Disease Neuropathology and Dietary Intake of Seafood Between Seafood Intake Groups ( $\geq 1$  meal/week vs.  $< 1$  week) and APOE  $\epsilon 4$  Status**

AD Neuropathology	APOE $\epsilon 4$ positive	APOE $\epsilon 4$ negative
Global AD Pathology $\beta$ (95% CI)	n = 65 -0.77 (-1.53 to -0.01)	n = 221 0.13 (-0.30 to 0.55)
Neuritic Plaque Density $\beta$ (95% CI)	n = 65 -0.69 (-1.34 to -0.04)	n = 218 0.26 (-0.14 to 0.65)
Neurofibrillary Tangle Severity $\beta$ (95% CI)	n = 65 -0.77 (-1.52 to -0.02)	n = 218 0.20 (-0.19 to 0.59)
Alzheimer Disease Diagnostic Score $\beta$ (95% CI)	n = 65 -0.53 (-0.96 to -0.10)	n = 218 0.20 (-0.04 to 0.43)

AD = Alzheimer's disease; 95% CI = 95% confidence interval

Adapted from: Morris MC, Brockman J, Schneider JA, et al. Association of seafood consumption, brain mercury level, and APOE  $\epsilon 4$  status with brain neuropathology in older adults. *JAMA* 2016; 315:489-497.

mcg/g in the midfrontal region and 0.87 (1.80) mcg/g in the cerebellum. Cortical brain mercury levels were positively correlated with cortical selenium levels ( $\rho$ , 0.35;  $P < 0.001$ ) and with the number of seafood meals consumed per week ( $\rho$ , 0.16;  $P = 0.02$ ). No significant correlation ( $P = 0.07$ ) was found between brain mercury levels and AD neuropathology. Brain mercury levels were significantly correlated with lower odds of macroinfarcts and microinfarcts ( $P = 0.05$  and  $P = 0.01$ , respectively), and brain selenium levels were not correlated with neuropathologic markers, except for neurofibrillary tangle severity in which higher selenium levels were correlated with higher tangle severity ( $P = 0.04$ ).

#### ■ COMMENTARY

It is estimated that more than five million Americans are suffering from AD, an incidence that is expected to rise to 13.8 million by 2050.<sup>2-5</sup> AD is the most common cause of dementia. The etiology of AD is not clearly understood and further research into both causative and protective factors is needed.<sup>2,4,5</sup> There are numerous risk factors for AD, the main ones being increasing age, APOE status, and female sex.<sup>2,4,5</sup> Other risk factors for AD include nutritional factors, low levels of physical activity, reduced cognitive stimulation, socioeconomic status and educational attainment, poor sleep quality, air pollution, smoking, intake of metals, pesticides and insecticides, and metabolic-related dysfunction.<sup>2,4,5</sup>

This study adds to the body of evidence demonstrating a beneficial effect of dietary patterns emphasizing vegetables and fish, such as the Mediterranean dietary pattern, with better cognitive health and a decreased risk of AD and/or dementia. According to the authors, this is the first published study that investigated the

relationship between diet, brain neuropathology, and brain concentrations of mercury. Also, this study included a large amount of brain autopsy data. The lack of association (positive or negative) between fish oil consumption and AD neuropathology is an important finding, not unlike a recent Cochrane review, which also found a lack of evidence to support n-3 PUFA supplementation as a treatment for mild-to-moderate dementia.<sup>4</sup>

Limitations of this study include the observational study design, which does not allow for determination of causality. The food frequency questionnaire is validated. However, it is a subjective measurement of the dietary intake of EPA, DHA, and  $\alpha$ -linolenic acids. The participants in this study were mostly non-Hispanic white older adults who lived in Chicago and ate a moderate amount of seafood, so the findings cannot be generalized to other populations with higher seafood consumption or with high mercury exposure. The authors also mentioned that there was insufficient statistical power to detect small correlations of n-3 PUFA on neuropathology in the APOE  $\epsilon 4$  positive group.

Another limitation of this study is the lack of data of other genetic mutations that are known to increase the risk of AD. Although the APOE  $\epsilon 4$  allele increases the risk of developing AD, it is not predictive of developing AD.<sup>6</sup> Individuals without the APOE  $\epsilon 4$  allele who have a first-degree relative with AD still have a two- to four-fold increase in risk of developing AD. The American College of Medical Genetics (ACMG) recommends genetic testing of a number of genes involved in AD if the patient is symptomatic.<sup>6</sup> However, APOE genetic testing is not routinely recommended because it has a poor predictive value alone. The ACMG recommends that patients who are symptomatic

or have a family history of AD should be referred to a genetic counselor. Direct-to-consumer APOE genetic testing is not recommended.<sup>6</sup>

Recommending a diet with moderate fish consumption may be beneficial to aging patients. Counseling patients about the benefits of eating sustainable fish with lower mercury levels is also important when recommending moderate fish consumption. Such data are provided by Seafood Watch.<sup>7</sup> Mercury in fish exists mostly in the form of methyl mercury and has been found to be highly variable even within a given fish species.<sup>8</sup> More studies evaluating the levels of mercury and other contaminants in seafood found throughout the world are needed to better estimate the levels of mercury in imported seafood and its effects on human health.<sup>8</sup> Although this study demonstrates benefit with eating one or more seafood meals per week, more research is required to further understand the role of n-3 PUFAs in cognitive health and AD neuropathology, as a number of other factors, including nutritional factors, low levels of physical activity, reduced cognitive stimulation, socioeconomic status and educational attainment, poor sleep quality, air pollution, smoking, intake of metals, pesticides and insecticides, and metabolic-related dysfunction, have demonstrated risk. Recommending a Mediterranean dietary

pattern with adequate physical activity, increased cognitive stimulation, adequate sleep, avoidance of smoking, and avoiding intake of metals, pesticides, and insecticides may be beneficial in decreasing cognitive decline and AD. Referring patients showing symptoms of AD or asymptomatic patients with a first-degree relative with AD or dementia to a genetic counselor is warranted. ■

#### REFERENCES

1. Riedel BC, Thompson PM, Brinton RD. Age, APOE and sex: Triad of risk of Alzheimer's disease. *J Steroid Biochem Mol Biol* 2016;160:134-147.
2. Kroger E, Laforce R Jr. Fish consumption, brain mercury, and neuropathology in patients with Alzheimer disease and dementia. *JAMA* 2016;315:465-466.
3. Genetics Home Reference. APOE. Available at: <https://ghr.nlm.nih.gov/gene/APOE#resources>. Accessed June 6, 2016.
4. Burckhardt M, Herke M, Wustmann T, et al. Omega-3 fatty acids for the treatment of dementia. *Cochrane Database Syst Rev* 2016;4:CD009002
5. Pistollato F, Ohayon EL, Lam A, et al. Alzheimer disease research in the 21st century: Past and current failures, new perspectives and funding priorities. *Oncotarget* 2016; doi: 10.18632/oncotarget.9175 [Epub ahead of print].
6. Goldman JS, Hahn SE, Catania JW, et al. Genetic counseling and testing for Alzheimer disease: Joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors. *Genet Med* 2011;13:597-605.
7. Seafood Watch. About Us. Available at: <http://www.seafoodwatch.org/about-us>. Accessed June 6, 2016.
8. Karimi R, Fitzgerald T, Fisher NS. A quantitative synthesis of mercury in commercial seafood and implications for exposure in the United States. *Environ Health Perspect* 2012;120:1512-1519.

## MORTALITY

### ABSTRACT & COMMENTARY

# Nature Nurturing Health

By Seema Gupta, MD, MSPH

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

SYNOPSIS: A national prospective cohort study of nurses found that higher levels of green vegetation were associated with decreased mortality.

SOURCE: James P, Hart JE, Banay RF, Laden F. Exposure to greenness and mortality in a nationwide prospective cohort study of women. *Environ Health Perspect* 2016 Apr 14 [Epub ahead of print].

For the first time in history, a majority of humanity is urbanized, with more than 50% of the planet's 7.1 billion people living in urban areas. As population and urban development increases at an unprecedented rate, it creates a tremendous stress on local, regional, and global air and water quality. Urbanization leads to land use and land cover change, which is a major driver of

global environmental change. The growing disease burden in urban areas attributable to nutrition and lifestyle choices remains a major public health challenge. For example, urbanization is associated with profound changes in diet and exercise that in turn increase the prevalence of obesity with attendant increases in risk of type 2 diabetes and cardiovascular disease.<sup>1</sup> Growing evidence

suggests close contact with nature benefits health. There is emerging research and policy interest in the potential for using the natural environment to enhance health and well being. Positive health effects of green space have been observed on cardiovascular diseases, mental health, self-reported general health, sleep patterns, and longevity, just to name a few.<sup>2</sup> Similarly, the use of green space has been associated with higher levels of physical activity and lower levels of obesity within communities.<sup>3</sup> Evidence also supports the hypothesis that living in areas with higher amounts of green spaces reduces mortality, mainly related to cardiovascular disease.<sup>4</sup> However, this evidence is limited in scope, and many studies have relied on aggregated data limiting inferences regarding the effect of greenness on individual health.

James et al used data from the Nurses' Health Study prospective cohort to examine greenness around the homes of 108,630 adult women. Researchers mapped home locations and used high-resolution satellite imagery to determine the level of vegetation within 250 meters and 1,250 meters of the homes. Researchers followed study participants between 2000 and 2008, tracking changes in vegetation and participant deaths. During the study, 8,604 participants died.

The authors analyzed models after adjusting for mortality risk factors such as age, race/ethnicity, smoking, and individual- and area-level socioeconomic status. Researchers found that women living in the highest quintile of cumulative average greenness (accounting for changes in residence during follow-up) in the 250 meters area around their homes experienced a 12% lower rate of all-cause, non-accidental mortality (95% confidence interval [CI], 0.82-0.94) compared to those in the lowest quintile. Results remained consistent for the 1,250 meters area, although the relationship was slightly attenuated.

Cause-specific mortality analyses demonstrated that the associations were strongest for respiratory, cancer, and kidney disease mortality. When researchers compared women in the areas with highest greenness to those in the lowest, they found a 34% lower rate of respiratory disease-related mortality (95% CI, 0.52-0.84), a 41% lower rate of kidney disease mortality (95% CI, 0.33-1.05), and a 13% lower rate of cancer mortality (95% CI, 0.78-0.97). Researchers did not note any statistically significant association between greenness and mortality from coronary heart disease, diabetes, or infections.

James et al suggested that a large proportion of the association between greenness and mortality may be explained through mental health pathways of depression risk and social engagement, which subsequently affects mortality.

#### ■ COMMENTARY

Going green could be good for health and society in many ways. This study was the first prospective examination of the relationship between exposure to greenness and mortality across the entire United States, and it demonstrated that nurses who lived in areas with more vegetation experienced lower death rates regardless of age, race/ethnicity, smoking, or socioeconomic status. The findings were consistent across all regions of the country (including urban and rural areas) and were most robust for cancer, respiratory, and kidney disease mortality. These findings substantiate previous research in the field.

Biophilia is a theory that suggests an instinctive bond between humans and other living systems; therefore, the theory suggests people have evolved to prefer certain natural environments that are essential to their prospering.<sup>5</sup> The findings of this study with regard to respiratory and cancer mortality benefits may be attributed to a reduction in air pollution exposure and increased physical activity in the areas of greater greenery. Renal disease mortality benefits also may be related to greater physical activity. Higher exposure to greenness consistently has been linked to lower levels of depression, anxiety, and stress. So it seems that greenness may lower all-cause as well as cause-specific mortality in women, which perhaps can be explained by benefits in mental health, social engagement, physical activity, and lowering of air pollution. If these findings are to be believed, and there is no reason they should not be, we may find ourselves giving recommendations for planting trees and other vegetation to our patients while saving the environment — something we never learned in medical school. ■

#### REFERENCES

1. Patil RR. Urbanization as a determinant of health: A socioepidemiological perspective. *Soc Work Public Health* 2014;29:335-341.
2. Nieuwenhuijsen MJ, Kruize H, Gidlow C, et al. Positive health effects of the natural outdoor environment in typical populations in different regions in Europe (PHENOTYPE): A study programme protocol. *BMJ Open* 2014;4:e004951.
3. Lachowycz K, Jones AP. Greenspace and obesity: A systematic review of the evidence. *Obes Rev* 2011;12:e183-189.
4. Gascon M, Triguero-Mas M, Martínez D, et al. Residential green spaces and mortality: A systematic review. *Environ Int* 2016;86:60-67.
5. Wilson EO. *Biophilia*. Cambridge, MA: Harvard University Press; 1984.

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## CME QUESTIONS

1. Which of the following is true regarding the long-term vegetable fat (either olive oil or mixed nuts) enrichment of a Mediterranean diet?
  - a. People in the olive oil group lost over 1 cm of waist circumference
  - b. People in the mixed nuts group gained slightly more weight than the control diet group
  - c. The olive oil group lost about 1/2 kilogram more weight than the control group.
  - d. Neither the olive oil nor the mixed nuts group showed any difference compared to the control group.
2. What were the results of the Attias et al study on the treatment of preoperative anxiety?
  - a. Standard benzodiazepines appeared to give the most immediate relief from self-awareness of anxiety, but had the most complications and side effects, including longer postoperative stays.
  - b. An individualized approach with low-dose benzodiazepines and acupuncture at selected points demonstrated reduction in pulse and blood pressure and shortened operative time.
  - c. The individualized integrative therapies selected for this study, in combination with low-dose benzodiazepines, were most effective at reducing self-awareness of state anxiety.
  - d. Listening to a generic recording of relaxation instructions prior to surgery showed no effect on reduction of preoperative anxiety.
3. Which of following is the best recommendation for patients with AD or at high risk for developing AD?
  - a. Recommending a diet high in seafood
  - b. Recommending a Mediterranean dietary pattern
  - c. Recommending increased  $\alpha$ -linolenic acid
  - d. Recommending a Mediterranean dietary pattern with seafood intake that is low in mercury and referral to a genetic counselor
4. Researchers found that higher levels of green vegetation were associated with lower mortality in all categories *except*:
  - a. respiratory disease.
  - b. renal disease.
  - c. cancer.
  - d. cardiovascular disease.

## 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.

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