

# Integrative Medicine

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

## FALLS

### ABSTRACT & COMMENTARY

## Mediterranean Diet and Frailty Risk

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

**SYNOPSIS:** The authors of a review and meta-analysis involving four studies and more than 5,000 community-dwelling adults over the age of 60 years concluded that greater adherence to the Mediterranean diet was associated with a reduced risk of frailty.

**SOURCE:** Kojima G, Avgerinou C, Iliffe S, Walters K. Adherence to Mediterranean diet reduces incident frailty risk: Systematic review and meta-analysis. *J Am Geriatr Soc* 2018; Jan. 11. doi:10.1111/jgs.15251. [Epub ahead of print].

Currently, the only available alternative to aging is death. However, development of frailty linked with aging may not be so inevitable. In fact, evidence is building that the onset of frailty, theoretically defined in 2011 as “a clinically recognizable state of increased vulnerability resulting from aging-associated decline in reserve and function across multiple physiologic systems,” has modifiable risk factors.<sup>1</sup>

Nutritional status is believed to play an important role in either development or protection from frailty.<sup>2</sup> However, it is not known if a specific diet or dietary pattern is key. Kojima et al noted that studies regarding the Mediterranean diet and frailty are few in number and have

produced mixed results. They believed a meta-analysis could assist in revealing more subtle relationships. After performing a systematic and extensive literature search, Kojima et al identified four studies meeting all criteria to include in the meta-analysis. These studies included 5,789 community-dwelling people ≥ 60 years of age. The mean follow-up time was 3.9 years. The included studies used the Mediterranean Diet Score (MDS)<sup>3</sup> to measure the degree of adherence to a traditional Mediterranean diet. Based on their scores on the MDS, respondents were grouped into one of three possible categories (0-3; 4-5; 6-9), with higher scores representing closer adherence to the diet. Each study used a food frequency questionnaire to record dietary choices.

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# Integrative Medicine

[ALERT]

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## Summary Points

- The authors of a literature review regarding adherence to the Mediterranean diet and frailty identified four studies involving 5,789 subjects that met criteria for inclusion in this meta-analysis.
- All included studies used the same scale to measure degree of adherence to the Mediterranean diet; the studies defined frailty using multiple criteria, such as unintentional weight loss, weakness, and slowed ambulation.
- In all studies, higher adherence to the Mediterranean diet and lower frailty risk were highly correlated.

To measure frailty, researchers used one of two standardized scoring tools. Both scales incorporated multiple criteria to assess degree of frailty. All four studies used odds ratios (OR) adjusted for multiple variables to represent the incident frailty risk.

Three studies were conducted in Southern Europe or Mediterranean Europe, and one study was from China. Notably, dietary patterns from the Mediterranean region are the foundation of the Mediterranean diet. Kojima et al wondered if the Chinese study, given the difference in native dietary habits, was skewing results. However, excluding the Chinese study did not change results substantially.

Table 1 shows the incident frailty risk in the pooled group of four studies when comparing higher adherents to the Mediterranean diet with lower adherents. The second portion of the chart shows incident frailty risk in the reduced pooled group to just the three studies performed in Mediterranean Europe (Chinese study excluded.) All ORs are adjusted for multiple variables or potential confounders, including sex and age of participants, marital status, use of medication, and health habits, such as use of tobacco products and/or alcohol.

## ■ COMMENTARY

The authors of this large meta-analysis looked at the results of four studies investigating adherence to the Mediterranean diet and frailty. A review of these terms — Mediterranean diet and frailty — may clarify the results and implications of the study.

The Mediterranean diet takes its name from its origins in lands surrounding the Mediterranean Sea. Well-known for many potential

health benefits, the Mediterranean diet is not a diet per se but a pattern of eating based on the traditional diet of this geographic region. Plant foods, such as vegetables, fruits, nuts, legumes, and seeds, are the base of the diet, with olive oil the primary source of fat. Dairy is limited and usually in the form of cheese and/or yogurt. Typically, fish is the most prominent animal food, followed by poultry and occasional red meat. Wine consumption is moderate and usually accompanies a meal.<sup>4</sup>

In all the studies in the meta-analysis, food consumption records were obtained via food frequency questionnaires. It is worth noting that the accuracy of these reports was determined in large part by memory and truthfulness of the participants. Future studies with more objective methods will be helpful in reaching a fuller understanding of the relationship between diet and frailty.

Frailty is a medical concept lacking a standard definition, but theoretically understood as a common geriatric syndrome with increasing prevalence with age. In 2001, Fried et al offered descriptive criteria now commonly accepted for use as a working definition to enhance the understanding of frailty. They identified five benchmarks: unintentional weight loss, exhaustion, deterioration in grip strength, slowed gait, and decreased physical activity. According to the Fried definition, three out of the five criteria must be present to diagnose and stage frailty. Thus, frailty is distinct from comorbidities and disability rather than synonymous with these conditions, as had been postulated up until Fried's work. In fact, we now understand that disability may result from frailty and that comorbidities contribute to this condition.<sup>5</sup>

**Table 1: Odds Ratio of Incident Frailty Risk**

	<b>4-5 MDS vs. 0-3 MDS (higher score = closer adherence to diet)</b>	<b>6-9 MDS vs. 0-3 MDS (higher score = closer adherence to diet)</b>
Incident Frailty Risk: Pooled odds ratio (4 studies)	0.62 (95% CI, 0.47-0.82)	0.44 (95% CI, 0.31-0.64)
<i>P</i> value	0.001	< 0.001
Incident Frailty Risk: Pooled odds ratio for Mediterranean Europe studies (excluding Chinese study)	0.60 (95% CI, 0.44-0.82)	0.40 (95% CI, 0.27-0.65)
<i>P</i> value Mediterranean Europe studies (excluding Chinese study)	0.001	0.001
MDS: Mediterranean diet score; CI: confidence interval		

A working operational definition allows systematic investigation of frailty risk factors and outcomes. Frailty itself is a risk factor for many poor health outcomes, including complications in hospitalized patients, earlier death, and poorer quality of life. Although the etiology, development, and progression of frailty appear to be complex and multifaceted, studies looking at improving nutritional state consistently are promising. Researchers have studied enhancing protein status and micronutrient load (carotenoids and vitamins).<sup>6</sup>

Although frailty may seem similar to failure to thrive (FTT), frailty is better understood as a contributor to this potentially more fulminant condition. FTT, defined as a “syndrome of weight loss, decreased appetite and poor nutrition, and inactivity, often accompanied by dehydration, depressive symptoms, impaired immune function, and low cholesterol” resides further along a spectrum that may result in full dependence and/or death.<sup>7</sup>

Estimates of prevalence of frailty vary according to population (institutionalized vs. community-dwelling, for example) and gender. Conservative estimates are that frailty affects about 10% of persons ≥ 65 years of age (15% of those 80 to 85 years of age and 26% of those > 85 years of age). Given these numbers, understanding and identifying prevention factors could affect public health costs significantly.<sup>8</sup>

The investigations included in this meta-analysis all attempted to go beyond looking at a specific food item or nutrient and focused instead on total intake or dietary pattern. While this makes sense intuitively given what we know about the interplay of micro- and macronutrients, it makes interpreting the results for clinical use a bit more challenging. Although we can tell patients that following a Mediterranean diet is associated with a lower risk of frailty, these studies do not allow an understanding of which elements of this diet are most crucial to protection. Kojima et al postulated that the antioxidant load in the abundant fruits and vegetables at the heart of the

Mediterranean diet may be a key factor in defeating frailty development. Clearly, future studies elucidating this most likely multifactorial relationship are essential.

Kojima et al met their goal of performing a meta-analysis to better understand the relationship between adherence to the Mediterranean diet and development of frailty. Incorporating multiple studies allows sufficient numbers of participants to interpret results with confidence, at least for the included populations. The results are impressive and show a close to linear reduction of frailty risk with higher adherence to a Mediterranean diet. Presenting these results in graphic form may serve as “food for thought” for older patients looking for dietary guidance.

One limitation of this meta-analysis is that only four studies were included. Although numbers of total participants are high, having few studies makes generalization of the results to all geographic and ethnic populations difficult. Cultural beliefs and food availability influence dietary patterns. The inclusion of a Chinese study in the meta-analysis is impressive in that it lends confidence that these results may be transferable across cultural barriers. However, incorporating many cultures and backgrounds will be important to present these results with full confidence.

Another interesting aspect of these studies is that diet information was collected at the onset of the investigations when (by definition) all participants were ≥ 60 years of age. We do not have information about dietary habits prior to this age. A long-standing dietary pattern may be influential on frailty development, but we are not able to conclude or extrapolate from the provided information.

Certainly, for now, explaining the highlights of a Mediterranean diet to patients at risk for development of frailty falls squarely into the category of good preventive medicine. Notably, this risk pool includes all patients > 60 years of age. A Mediterranean diet pyramid for distribution in the office is a readily available tool for review

of diet components.<sup>8</sup> Finally, explaining to patients that there is no evidence of an “all or none” phenomenon with this eating pattern should be reassuring. Informing patients that a shift toward greater adherence to this dietary pattern may be associated with maintaining strength while aging can be instrumental in helping the patient view a change in dietary habits as possible rather than formidable. ■

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## PAIN

### ABSTRACT & COMMENTARY

# Medical Cannabis and Chronic Pain

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

**SYNOPSIS:** The authors of this systematic review investigating the effects of medical cannabis (MC) on chronic pain in adults found that there is limited evidence to support the use of MC in treating neuropathic pain and that there is insufficient evidence that MC improves other types of chronic pain.

**SOURCE:** Nugent SM, Morasco BJ, O'Neil ME, et al. The effects of cannabis among adults with chronic pain and an overview of general harms: A systematic review. *Ann Intern Med* 2017;167:319-332.

**C***annabis sativa* and *Cannabis indica* increasingly are becoming available for both medical and recreational use in the United States, with chronic pain one of the most cited reasons for medical use.<sup>1</sup> In 1999, California was the only state in which medical cannabis (MC) was legal, and by 2018, MC was legal in 29 states and recreational cannabis was legal in nine states (Alaska, California, Colorado, Oregon, Massachusetts, Maine, Nevada, Vermont, and Washington).<sup>2</sup> Although several states have deregulated cannabis use, the federal government has not followed suit and cannabis remains a Schedule 1 (no known legal medicinal use) substance. Individuals suffering from chronic pain conditions increasingly present to their healthcare providers wanting to discuss using MC to treat their pain. A recent study investigating U.S. physician attitudes toward MC found that 89.5% of surveyed residents and fellows did not feel prepared to prescribe MC and only 35.3% reported readiness to answer questions regarding MC.<sup>3</sup> Only 9% of U.S. medical schools reported clinically relevant MC content in their curriculum.<sup>3</sup>

To further elucidate whether there is evidence to recommend MC in the treatment of chronic pain and whether

### Summary Points

- Cannabis plants contain two primary physiologically active compounds: tetrahydrocannabinol and cannabidiol.
- Between 45% and 80% of individuals who use medical cannabis do so for pain management.
- Insufficient evidence exists to make a good recommendation regarding the use of medical cannabis for the treatment of pain.

there are harms associated with its use, Nugent et al further examined the evidence in a systematic review. This study included English-language studies investigating the effect of plant-based cannabis or whole plant extracts on chronic pain in non-pregnant adults. The authors defined plant-based cannabis preparations to include any preparation of the cannabis plant or extracts to capture the variety of products available in U.S. dispensaries. (See *Table 1*.)

**Table 1: Cannabis Types Studied and Available in U.S. Dispensaries**

Type of Medical Cannabis	Number of Studies
Nabiximols	12
Smoked THC	5
THC/CBD capsules	3
Vaporized THC	3
Orally ingested, standardized THC product	2
Sublingual spray	1
Oral mucosal spray	1

THC: tetrahydrocannabinol; CBD: cannabidiol

The authors also included studies of nabiximols, which is a cannabis extract that is standardized to deliver 2.7 mg of tetrahydrocannabinol (THC) and 2.5 mg of cannabidiol (CBD) through an oral mucosal spray. The authors identified potential studies to be included in this systematic review through MEDLINE, Embase, PubMed, PsycINFO, Evidence-Based Medicine Reviews, and gray literature sources from database inception until February 2016. The authors then updated this search in March 2017 to identify any new randomized, controlled trials and other systematic reviews. The authors also identified ongoing studies through ClinicalTrials.gov, the International Clinical Trials Registry Platform, the National Institutes of Health RePORTER, and the Agency for Healthcare Research and Quality Grants On-Line Database.

A total of 13,674 studies were identified; 12,460 studies were excluded because they were not relevant to this review and another 1,139 studies did not meet inclusion criteria. (See Figure 1.) Of the 75 publications included in this systematic review, 32 studies were included in the chronic pain analysis and 43 studies were included in the harms analysis. Two investigators abstracted details of study design, setting, patient population, intervention, and follow-up, as well as important co-interactions, health outcomes, healthcare use, and harms. Each trial was assessed as having low, high, or unclear risk of bias (ROB) for the pain outcomes by two reviewers using an outcome tool developed by the Cochrane Collaboration. Disagreements were resolved by consensus. Statistical heterogeneity was assessed using the Cochran chi-square test. All analyses were performed using Stata/IC version 13.1. For the subgroup of neuropathic pain, a meta-analysis was performed and the profile-likelihood random-effects model was used to perform the risk ratios. A meta-analysis on the other subgroups could not be performed because of heterogeneity, variation in outcomes reported, and the small number of trials, so these were reported qualitatively. The authors discussed the evidence for these subgroups and classified the overall strength of evidence for each outcome as high, moderate, low, or insufficient

based on the consistency, coherence, and applicability of the body of evidence as well as the internal validity of individual studies.

### NEUROPATHIC PAIN

Thirteen studies investigated the effects of MC preparations on neuropathic pain. Eleven were considered to have low ROB, one had unclear ROB, and the other had high ROB. The authors found low strength of evidence that MC may alleviate neuropathic pain in some patients. In nine studies, patients using cannabis to treat neuropathic pain were more likely to report at least a 30% improvement in pain (risk ratio, 1.43; 95% confidence interval [CI], 1.16-1.88;  $I^2 = 38.6$ ;  $P = 0.111$ ), although these results were not statistically significant.

### MULTIPLE SCLEROSIS

There were nine trials investigating the effects of cannabis on pain among patients with multiple sclerosis (MS). Three were considered to have low ROB, five had unclear ROB, and one had high ROB. The authors determined that they were unable to find sufficient evidence to characterize the effects of MC on pain in patients with MS. Among the three low ROB studies, one demonstrated no difference in outcome with cannabis, another found a small but clinically nonsignificant alleviation of pain at five weeks, and the authors of a trial with more participants found that more patients in the MC group reported decreased pain at 12 weeks compared to the control group (28.0% vs. 18.7%;  $P = 0.028$ ).

### CANCER PAIN

Three trials ( $n = 547$ ) investigated the effects of cannabis extracts on pain in cancer patients. The authors concluded that there was insufficient evidence because of the small number of studies and their methodological limitations.

### OTHER OR MIXED PAIN CONDITIONS

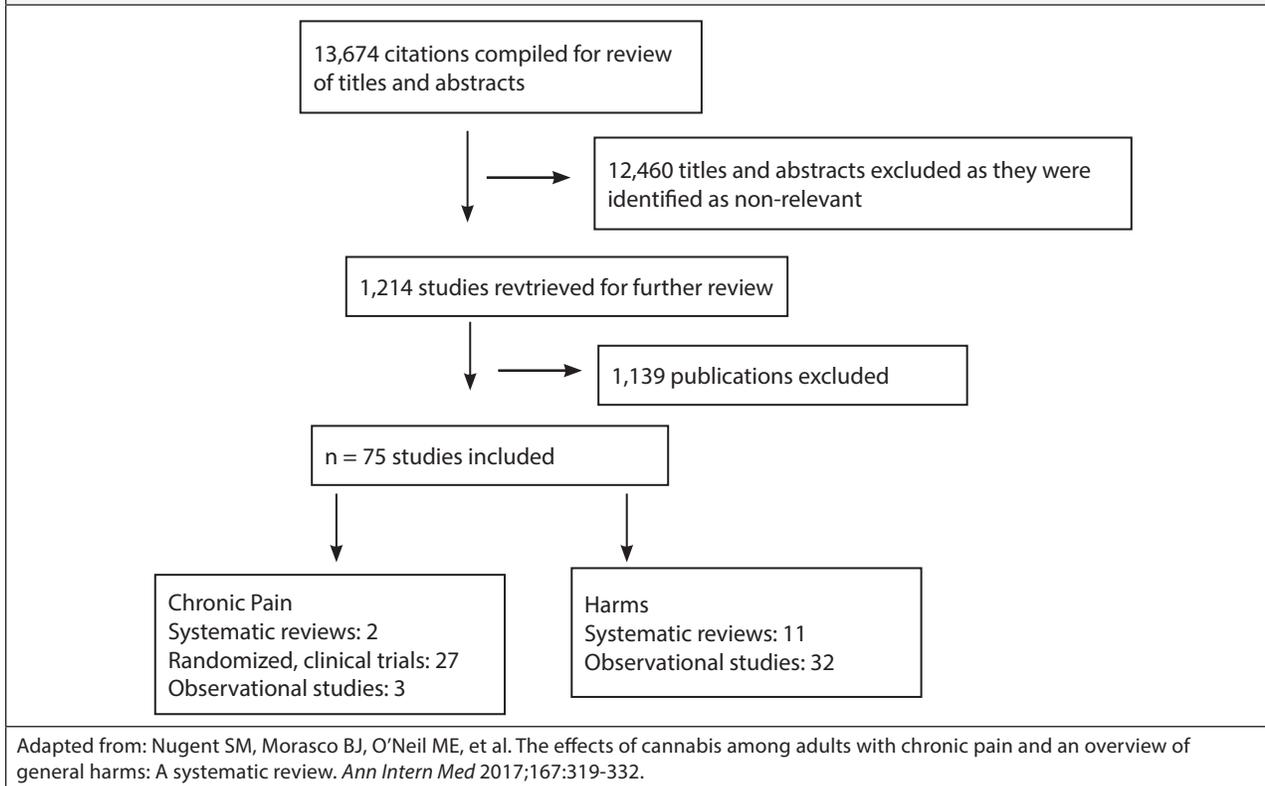
The authors of two trials and three cohort studies concluded that there was insufficient evidence because of methodologically flawed studies.

### HARMS OF CANNABIS USE

Adverse effects reported in two systematic reviews of cannabis use in chronic pain patients included dizziness and light-headedness, while other more serious side effects included suicide attempts, paranoia, and agitation. A prospective observational study did not find a difference between the cannabis group (12.5%  $\pm$  1.5% THC, 2.5 g/d) and the control group (adjusted incidence rate ratio for event, 1.08; 95% CI, 0.57-2.04).<sup>4</sup>

In the general population, two well-designed cohort studies indicated that low levels of cannabis smoking did not affect lung function adversely over about 20 years in young adults.<sup>5,6</sup> In eight studies and one systematic review, researchers found an association between the

**Figure 1: Data from Systematic Review of Cannabis**



development of psychotic symptoms and cannabis use. These psychotic symptoms were related to the strength of the THC content. The risk of developing psychosis with MC use is similar for the general population and those with a prior history of psychological conditions. The authors of a recent meta-analysis that included 21 multinational observational studies suggested that acute cannabis intoxication was associated with a moderate increase in motor vehicle collision risk (odds ratio [OR], 1.35; 95% CI, 1.15-1.61).<sup>7</sup>

Cannabinoid hyperemesis syndrome is a severe form of cyclic vomiting that has been associated with long-term cannabis use and acute cannabinoid toxicity. Aspergillosis and tuberculosis also have been associated with smoking cannabis. There is mixed evidence about whether cannabis has an effect on violent behavior. Cannabis use disorder, which is defined in the *Diagnostic and Statistical Manual of Mental Disorders 5* as a problematic pattern of cannabis use, is associated with cannabis use (adjusted OR, 9.5; 95% CI, 6.4-14.1) in a prospective cohort study (n = 34,653).<sup>8</sup> In a cross-sectional study of daily opioid therapy for chronic pain and cannabis use disorder, the prevalence was 2.4%, and 13.2% of patients reported using cannabis in the previous 30 days.<sup>9</sup>

#### ■ COMMENTARY

An increasing number of patients are using MC to treat chronic pain. In states in which recreational cannabis is legal, patients do not require a recommendation from

their healthcare provider. However, patients ask questions regarding the use of MC to treat their chronic pain, and because of insufficient evidence, healthcare providers often are unable to make evidence-based recommendations. Nugent et al sought to provide further clarification. Unfortunately, because of the quality of the original research studies, the authors only could perform a meta-analysis on the treatment of neuropathic pain with MC, which showed a reduction in pain and was not significant. Adverse side effects also were investigated, and cannabis use was significantly associated with cannabis use disorder. More research needs to be conducted to further understand the risk of adverse side effects from use MC.

This study was part of a larger investigation commissioned by the Veteran's Health Administration. A protocol was posted to a public website prior to the study initiation. The strengths of this systematic review are the selection of studies to be included in this analysis. Although the authors' review did not demonstrate a significant effect in using cannabis preparations for chronic pain, a report released by the National Academy of Sciences (NAS) differs in its level of significance.<sup>2</sup> The NAS report concluded that cannabis use to treat chronic pain has conclusive or substantial evidence of effect, with plant-derived cannabinoids 40% more likely to reduce pain than the control agent (odds ratio, 1.41; 95% CI, 0.99-2.00); of note, this is marginally statistically significant. Both the NAS and Nugent et al reviews included essentially the same trials, but the NAS report

**Table 2: Cannabis Products Available at Dispensaries and Route of Administration**

Route of Administration	Method	Types of Cannabis Products
Inhaled	Smoking, vaporizing, vape pens	Cannabis flower, oil, wax, resins, concentrates
Oral	Ingestion Sublingual and submucosal application	Candy, chocolate, baked goods, flavored soda, encapsulated extracts, tinctures, infused food stuffs (honey, butter, oil, etc.)
Transdermal	Topical application on skin	Oils, creams, ointments
Other	Suppositories	Encapsulated oil

found a more favorable effect of MC on chronic pain.<sup>2</sup> It is unclear how to interpret these disparate results other than to say that even the experts disagree.

There are many limitations to this systematic review, including the lack of methodologically sound studies, lack of studies in general, heterogeneity, and increased levels of ROB. Another important variable that may have influenced the results greatly are the cannabis preparations that were used.<sup>10</sup> Of the 27 RCTs included in the analysis of effects of cannabis for treating chronic pain, 12 used the cannabis extract nabiximols, five used smoked THC, three used THC/CBD capsules, three used vaporized THC, two used an orally ingested standardized THC product, one used a pump-action sublingual spray, and one used an oral mucosal spray with 2.7 mg of THC. There also was a wide range of study length, from one day to 15 weeks. The variation in cannabis preparations and method of administration may have a large effect on the results of the individual studies.<sup>10</sup>

Much of the research on the therapeutic effects of cannabis have used cannabis preparations that are pharmaceutical cannabinoids — dronabinol, nabilone, and nabiximols.<sup>1,2,10</sup> This is a major barrier to extrapolating the conclusion of these studies to patients, as many patients are interested in using or currently using cannabis products obtained from dispensaries. (See Table 2.) For example, CBD oil is becoming increasingly popular, but it is difficult to know whether studies on pharmaceutical-grade products or whole cannabis leaf products equate with what is available as a dietary supplement.

Furthermore, because cannabis is a Schedule 1 substance, it is difficult to obtain to use in research studies and this is one barrier to cannabis research.<sup>1,2,3</sup> Another important factor in cannabis research is that the DEA and FDA have only allowed researchers to use cannabis that was from the University of Mississippi; it was not until 2016 that researchers were allowed to begin to use other sources of cannabis. Although there is a lack of quality evidence to support MC use in chronic pain, one should not equate this lack of evidence to trial data suggesting no effects at this time.

#### BOTTOM LINE

Currently, there is limited evidence to support the use of cannabis in chronic pain management. However, it is still in the early stages of research, and more methodologically sound trials need to be conducted before we can make good evidence-based recommendations and understand the risks and benefits of use.

Until such evidence arises, clinicians should understand that patients are counseled about which MC products to use by employees who work in the MC or recreational cannabis stores, and that these employees may or may not have received adequate training. Because of the extensive choices available, it is important that healthcare providers be involved in this decision-making process.<sup>10</sup>

Adverse events have been demonstrated in patients who consume higher amounts of THC, especially if they have never used or are infrequent users of cannabis. There is a wide range of MC products, and some contain large amounts of THC, which patients should be counseled against using. Patients should be counseled that when inhaling through smoking or vaporizing, the effects are noticed within five to 10 minutes, but when ingesting orally it may take up to one to three hours for the MC to take effect.

As with all treatment recommendations, patients should be counseled about their chronic pain treatment options, including discussion about strength of the evidence, risks, and benefits. An additional consideration of which patients may not be aware is that since many employers still require employees to undergo drug testing, if they test positive for MC their position could be terminated. Shared decision-making techniques should be used in the discussion of whether patients should consider incorporating MC into their treatment plan. If patients want to use MC, providers should counsel them to choose a product that is lower in THC and contains CBD in as close to a 1:1 ratio or a CBD predominant chemovarietal product.<sup>10</sup> There is a great variation in individual sensitivities to the THC level in MC, and patients should be advised when ingesting edibles to start at a lower dose, such as 2.5 mg or less, and gradually increase the dosage

over days to weeks to the lowest dose that produces a therapeutic effect.<sup>10</sup> There is a large variation in the effects between different cannabis plants and preparations, which may be a result of both the types of CBD and the concentrations in the products.<sup>10</sup> Informing patients of these differences is helpful so that they can make an informed decision about MC use. ■

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## NUTRITION

### ABSTRACT & COMMENTARY

# Cardiovascular Nutrition Demystified

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

**SYNOPSIS:** The authors of this review of key nutritional studies compiled evidence-based information on foods and dietary patterns that support cardiovascular health and demystified those that have incorrectly been identified as beneficial to cardiovascular health.

**SOURCE:** Freeman AM, Morris PB, Barnard N, et al. Trending cardiovascular nutrition controversies. *J Am Coll Cardiol* 2017;69:1172-1187.

The foundation for prevention of atherosclerotic cardiovascular disease is a heart-healthy diet. Freeman et al examined data from more than 30 countries and included a variety of studies — meta-analyses, systematic reviews, randomized, controlled trials (RCTs), case control studies, and cohort studies — to shed light on the evidence for recommending particular foods and the reasons for the hype surrounding certain diets.<sup>1</sup> (See Table 1.)

**Eggs and Dietary Cholesterol.** Consumption of cholesterol increases the blood serum cholesterol, with each 100 mg increment in dietary cholesterol increasing total cholesterol by 2.2 mg/dL. After reviewing a meta-analysis of 17 studies examining the effects of eggs and cholesterol, the authors recommended that clinicians should continue to advise patients to reduce dietary cholesterol intake.

**Vegetable Oils: Not All Oils Are Created Equal.** It is generally assumed that plant-based oils are healthier than animal-based oils. However, not all plant oils are created equally, as they contain varying amounts of fatty acids, including saturated fatty acids (SFAs), polyunsaturated fatty acids (PUFAs), and monounsaturated fatty acids (MUFAs) even within the same family. When oils high in

### Summary Point

- Popular media has identified certain food groups as having cardiovascular health benefits.

MUFAs and PUFAs are used as a substitute to other saturated fats, there is a reduction in low-density lipoprotein cholesterol (LDL-C) levels, although there are no data on cardiovascular disease (CVD) outcomes. Although healthier substitutes of virgin coconut oil retain the bioactive polyphenols lost in refinement and have been promoted for cardiovascular benefits, no well-designed studies have shown evidence of CVD benefit from virgin coconut oil consumption. In addition, this oil contains high amounts of SFAs and, therefore, should be avoided. Ecological data of Asians who consume coconut as a staple show low incidence of atherosclerotic CVD. However, these populations also are consuming lower quantities of SFAs in general. Palm oil is high in SFAs and, thus, is not a heart-healthy oil and should be avoided. Plant and animal oils high in saturated fatty acids should

**Table 1: Recommendations for Foods to Consume Frequently, in Moderation, and to Avoid**

Consume Frequently	Consume in Moderation	Avoid Consuming
Green leafy vegetables: Evidence from large meta-analyses and variably sized observational studies	Nuts: Evidence from randomized, controlled trials (RCTs), prospective studies showing improved cardiovascular disease (CVD) outcomes	Coconut oil: Evidence from RCTs, meta-analyses, and observational studies on adverse lipid effects. No studies conducted to assess CVD outcomes
Protein from plant sources: Evidence from observational and prospective studies	Olive oil: Evidence from RCTs showing improved CVD outcomes	Antioxidant supplements: Evidence from RCTs, observational and prospective studies
Antioxidant-rich fruits and vegetables: Evidence from RCTs, and observational studies: Improved CVD outcomes and lipid profiles	Canola oil: Evidence from RCTs and meta-analyses showing improved lipids but no studies for CVD outcomes	Palm oil: Evidence from RCTs and observational studies
	Sunflower: No evidence for CVD outcomes	Southern diet pattern (fried foods, added fats, eggs, processed and organ meats) Evidence from prospective studies
* Limit dietary cholesterol: Evidence from RCTs		
* Gluten-containing foods should be avoided only if sensitive or allergic		

be replaced with oils high in PUFAs or MUFAs to help lower LDL-C.

In general, the issue of plant vs. animal is a result of the varying percentage of PUFAs and MUFAs. Freeman et al only discussed the differences between the plant-based SFAs and reminded people that just because the oil is derived from a plant does not mean it is healthy.

The cardioprotective effect of olive oil has been assessed in RCTs examining both outcomes and CVD biomarkers. Freeman et al reported that olive oil's effect for cardioprotection may be due to its polyphenol content. In addition, they reported that participants in the PRE-DIMED study had mean 30% reduction in the primary endpoint of composite of myocardial infarction, stroke, and CVD death, hence providing first level evidence of the health benefits of extra virgin olive oil (~4 tablespoons per day).

**Antioxidants: Whole Foods or Supplements.** Anthocyanins are highly concentrated in purple eggplant, red cabbage, red radishes, strawberries, and blueberries. Data from the Nurses' Health Study among postmenopausal women showed a trend toward decreased myocardial infarction risk and statistically significantly lower blood pressure in those who consumed about 1 cup of blueberries a day. However, excess antioxidant supplementation can lead to neutral or negative health effects because of a process known as hormesis, whereby substances are effective at low doses but are ineffective or harmful at higher doses. Therefore, the authors noted that fruits and vegetables provide the healthiest, most beneficial source of antioxidants.

**Nuts.** Freeman et al reported that large, prospective studies demonstrated the consistent cardioprotective effect of

nut consumption (four servings of nuts/week) on CVD outcomes. However, since nuts are calorie dense, portion control is key to prevent excess caloric intake.

**Green Leafy Vegetables.** Dark green leafy vegetables contain inorganic nitrate, which is converted to nitrite by salivary amylase, followed by acidification in the stomach to nitric oxide. Significant decreases in mean systolic blood pressure (-7.5 mmHg), which peaked at two hours postprandial, were observed in people who consumed 8.8 ounces of dark green leafy vegetables. Celery contains a vasodilator (3-n-butylphthalide) and has been found to decrease blood pressure in people with hypertension. Lutein, another component of dark green leafy vegetables, is inversely associated with incident hypertension. A diet rich in a variety of green leafy vegetables has a significant beneficial effect on atherosclerotic CVD risk and can be recommended to patients on warfarin, provided intake is consistent.

**Plant-based Diet.** Freeman et al noted that RCTs and epidemiological studies support that plant-based diets are associated with improvement in atherosclerotic CVD risk factors. For example, in the European Prospective Investigation into Cancer and Nutrition, vegetarians (avoid animal products, but some dairy products and eggs) had lower systolic blood pressure and a 32% lower risk of developing coronary heart disease. Populations, such as the Seventh-day Adventists, Okinawans, rural Chinese, central Africans, Papua New Guinea highlanders, and Tsimané, who predominantly consume a plant-based diet, rarely develop CVD. In a European study, vegetarians had a lower HDL-C.

**Gluten.** For those without a true gluten sensitivity or allergy, Freeman et al found the claims of health benefits for avoiding gluten are unsubstantiated.

## ■ COMMENTARY

The compilation of evidence-based information from various studies around the world supports that a diet rich in whole plant-based foods with limited quantities of animal products and oils decreased the risk of atherosclerotic CVD. The main strength of this study is that the authors examined data from studies worldwide, including Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy (39 countries), the U.S. Nurses' Health Study, and the Prevención con Dieta Mediterránea (Spain). There are challenges in studies of dietary patterns because of various factors: 1) Most use self-reporting, which may lead to under- or over-reporting certain foods; 2) There are confounders: People who eat certain foods also tend to exhibit certain behaviors that may affect the outcome; and 3) Researchers may not be measuring the factors that directly influence the outcome, but rather may be measuring the influencers.

A key challenge of epidemiological data is the risk of ecological fallacy; conclusions obtained from populations may not be true for individuals. Because of genetic differences, an emphasis on particular lifestyle recommendations may be even more important in some individuals than others. For example, certain people genetically remove cholesterol from serum more quickly than others, while other people with APOA1 single nucleotide polymorphism have higher levels of HDL-C4. This ability for cholesterol efflux is dependent on the functional capability of HDL and not just the quantity of HDL. Individuals with the same HDL levels may have different functional capacities of HDL. Other investigators have studied the serum cholesterol efflux capacity of HDL.<sup>2,3</sup> Khera et al showed that the greater the efflux capacity of HDL, the lower the prevalence of coronary artery disease.<sup>4</sup> Therefore, two individuals with the same quantitative HDL but differing functional capabilities of HDL most likely would need different nutritional advice. This may be the future of medicine: targeted and individualized nutritional recommendations based on evidence-based medicine.

This study very briefly touched on genetic differences in intestinal cholesterol absorptive capabilities that led to varied increase of total cholesterol with the same amount of dietary cholesterol. Some individuals had a greater increase in the measured cholesterol than others even with the same increase of dietary cholesterol. It is important for providers to retain a suspicion for a varied genetic response to dietary changes.

Part of the challenge of offering nutritional recommendations is that often providers do not know the key genetic differences of their patients. It will be interesting to see how the nutritional recommendations change as our understanding of cholesterol mechanisms improves. It is important for providers to expect that some of these recommendations will change as our understanding continues to evolve and to keep up to date with the changes. Current evidence shows that diets rich in whole foods from vegetables, fruits, and plant protein are naturally low in saturated fatty acids and are associated with a decreased atherosclerotic CVD risk. There are many fad diets and myths about healthy foods; therefore, it is important for providers to stay up to date on the latest evidence. In summary, this review of the current fad diets provides clear evidence for clinicians to engage in discussions with their patients, emphasizing that the certain foods — whole foods, vegetables, fruits, and plant protein — likely will have a positive effect on atherosclerotic CVD risk factors. ■

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## NUTRITION

### SHORT REPORT

# A Twist in the Use of Spices: Prebiotic Effect

By David Kiefer, MD, Editor

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

SYNOPSIS: Seven spices were found to contain numerous antioxidant phytochemicals and have an overall, but variable, prebiotic effect on 88 known species of microbiome bacteria.

SOURCE: Lu QY, et al. Prebiotic potential and chemical composition of seven culinary spice extracts. *J Food Sci* 2017;82:1807-1813.

The recent scientific literature has highlighted the physiological effect of spices focusing on their antioxidant and anti-inflammatory effects. This review, alternatively, ties spices into the burgeoning field of the microbiome, using a prebiotic mechanism as the connection. The researchers tested seven spices (black pepper, cayenne pepper, cinnamon, ginger, Mediterranean oregano, rosemary, and turmeric) and documented their chemical composition, antioxidant effect, and possible prebiotic effects. The authors defined prebiotics as "...substances that induce the growth or activity of microorganisms that contribute to the well-being of their host."

The researchers extracted each of the plants in hot water (presumably, at least partly replicating a culinary use) and tested those extracts on 88 species of bacteria found in the large intestine (representing the microbiome) to determine the Minimum Inhibitory Concentration (MIC). The MIC was the lowest concentration found to result in no growth or a "marked change" in the appearance of growth as compare to control agar growth plates. The "marked change" could indicate growth stimulation, which they would document. They found that all plants, except turmeric, promoted the growth of Bifidobacteria and Lactobacillus species ("good" bacteria), whereas all seven plant extracts inhibited the growth of Ruminococcus species (a "bad" bacteria). There were variable effects on two other "toxigenic" genera, Clostridia and Fusobacteria. (See Table 1.) In the paper, large tables with MIC details are presented, the accuracy of which is to be perhaps doubted; the abstract states that cinnamon, oregano, and rosemary inhibit Fusobacteria, whereas the text states that cinnamon, ginger, and oregano have inhibitory effects (their Table 3 supports the abstract). Surely, it is difficult to keep track of the effect of seven plants of varying concentrations on 88 bacteria.

There are a multitude of antioxidant tests available, but in this study, the researchers used the Trolox equivalent antioxidant capacity (TEAC), for reasons that were not documented. Of the seven plants, rosemary and oregano were found to have the highest antioxidant effect by this assay, and ginger the lowest, ranging from 140.4 to 13.1 millimolar trolox equivalents. The researchers also found

## Summary Point

- Seven spices were tested on a variety of gut flora and found to have a mostly growth-promoting effect on beneficial bacteria and an inhibitory effect on toxigenic, or "bad" bacteria.

that the antioxidant effects correlated directly with the total chemical composition. On this note, the researchers quantified the total concentration of phenolic and other compounds in each of the plant samples. Phenolics are a well-known family of compounds thought to have physiological, and resulting clinical, effects. The specific compounds were identified using high-performance liquid chromatography methods; 14 major phenolics were found in cayenne pepper, ginger, oregano, rosemary, and turmeric, while piperine, an alkaloid, was found in black pepper, and cinnamic acid and cinnamaldehyde were found, not surprisingly, in cinnamon.

All told, these results are interesting by corroborating recent advancements in the knowledge that diet affects the microbiome, but taking it one more step. Prior to this, most dietary prebiotic effects were thought to be due to specific fiber and carbohydrate-containing foods; the fact that spices, plants used in small amounts to flavor or preserve food, also could have that effect is novel and potentially important.

What is unclear from this study is dose. Do the concentrations of the extracts used correspond to clinically significant changes in the diet with spice-concentration ingestion? Also, we know that some, mostly hydrophobic, compounds are not particularly well dissolved in aqueous solutions, and so may not be appropriately analyzed in this study. Furthermore, we don't always cook with a water base; thinking about oil-based foods and cooking methods, the next analysis might examine how those spices affect the microbiome when ingested in this way. We also might take issue with the antioxidant testing; it provides little new information and may not be accurate. There is controversy about the use of any antioxidant testing, so much so that a major scientific journal recently decided to not publish any antioxidant analyses.<sup>1</sup> The

**Table 1: The Effect of Seven Plant Extracts on Various Microbiome Species**

Plant	Bifidobacteria	Lactobacillus	Ruminococcus	Fusobacteria	Clostridia
Black pepper	+	+	-	NE	NE
Cayenne pepper	+	+	-	NE	NE
Cinnamon	+	+	-	-	-
Ginger	+	+	-	NE	NE
Oregano	+	+	-	-	NE
Rosemary	+	+	-	-	-
Turmeric	NE	NE	-	NE	-

Growth promotion (+), growth inhibition (-), and no effect (NE) are all detailed.

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antioxidant conclusions drawn by the authors probably should be taken with a grain of salt (pun intended). Finally, we should keep the researchers to task with their botanical identification; identification to species allows us to know exactly which plants were used in this study, but this information wasn't provided. There are many different culinary oregano species used, and at least two cinnamon species available in the marketplace; the next iteration of this work should provide the Latin scientific names of these to be complete.

The microbiome effects of diet, lifestyle, pharmaceuticals, and countless other variables, are complex, making it difficult to know exactly

what to tell patients in clinic. This paper seems to indicate an overall positive physiological effect of spices, at least in the laboratory. The next steps will be to determine the exact microbiome effects on individuals when those plants are ingested as spices in the short and long term. We may learn in the future that certain patients, with a certain microbiome environment, would benefit from the use of specific spices in specific doses. Until that scientific guidance arrives, there seems to be little harm in weaving in these plants, as spices, to our diet. ■

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### CME QUESTIONS

1. Which statement is most true regarding the meta-analysis about the Mediterranean diet and frailty?
  - a. Greater adherence to a Mediterranean diet was associated with a reduction in frailty among older persons living in a community setting in Southern Europe and China.
  - b. The Mediterranean diet was associated with many health benefits, including a reduction in frailty among those who strictly adhere to the dietary components.
  - c. There is clear evidence that adopting a Mediterranean-style diet at an early age leads to health benefits and reduces the risk of development of frailty after the age of 60 years.
  - d. Frailty is age-determined and inevitable; there are no modifiable risk factors to prevent development of frailty over time.
2. Which of the following statements is not true about cannabis?
  - a. CBD is the main psychoactive ingredient.
  - b. Cannabis is a Schedule I substance.
  - c. Patients seek cannabis as a treatment for pain.
  - d. There is insufficient evidence investigating cannabis as an effective treatment in pain to support recommending cannabis.
3. Which of the following statements is true?
  - a. Coconut oil is a healthy oil because of the content of bioactive polyphenols and, therefore, is recommended as a heart healthy oil.
  - b. Extra virgin olive oil with a high content of polyphenols is a healthy oil.
  - c. Extra virgin olive oil with low polyphenol content is a healthier option than olive oil with high polyphenol content.
  - d. Juicing is the best way to obtain the necessary antioxidants for all individuals.
4. Which of the following is true regarding the effect of the seven spices on microbiome bacteria?
  - a. All seven plants inhibited the toxigenic bacteria *Ruminococcus*.
  - b. Only turmeric promoted the growth of *Bifidobacteria*.
  - c. All seven plants promoted the growth of *Clostridia* species.
  - d. None of the plants had a measurable effect on bacteria growth.

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