

# Integrative Medicine

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

## DEPRESSION

### Saffron and Depression: What Do We Know and Where Do We Go?

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

**SYNOPSIS:** Saffron studies, while still preliminary, show potential for use of this ancient spice in combatting mild-moderate depression.

Phytotherapy, using scientific methods to determine appropriate and effective medicinal use of plant-derived medications, is of particular interest to integrative providers.<sup>1</sup> With recent studies showing promising results, saffron, from the dried stigma of a delicate crocus flower, has the potential to attract interest not only from phytotherapists, but also from the medical community in general.

Even with controlled studies, is Western medicine ready to integrate into the arsenal of medical treatment a spice that has been known for medicinal use in the Eastern world for thousands of years? More specifically, can one of the most expensive spices in the world be useful in the fight against depression, one of the costliest and debilitating conditions known to humanity? These are questions posed by researchers interested in the mode

of action, side effects, and efficacy of saffron in the treatment of depression. Current research certainly is promising, but conclusive, long-term studies still are necessary before firm recommendations regarding age, dosing requirements, and other specifics are available. However, knowledge regarding the background and origins of saffron, its historic role in Eastern medicine, the spread of its use to the Western world, and an up-to-date view of the most current studies regarding saffron is useful for providers when discussing this treatment option with patients.

#### ANTIDEPRESSANTS AND DEPRESSION

In 2013, the most recent year statistics are available, 12% of U.S. adults reported use of antidepressants. Notably, antidepressants are used to treat many disorders, including not only depression, but also anxiety, post-

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# Integrative Medicine

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## Summary Points

- Saffron, from the stigma of the *Crocus sativa* plant, has been used medicinally in the Eastern world for centuries.
- Researchers are investigating the use of saffron in mild-moderate depression.
- A meta-analysis from 2015 and several subsequent studies show promising findings, with saffron (15 mg twice daily) demonstrating efficacy similar to conventional antidepressants in treatment of mild-moderate depression.
- Side effects, long-term effects, and use in special populations remain under investigation.

traumatic stress disorder, chronic pain, and mood disorders.<sup>2</sup> The estimates for a diagnosis of adult depressive disorders number close to 16 million adults per year, or 6.7% of all U.S. adults.<sup>3</sup> The global burden of depression is even more worrisome — according to the World Health Organization, 350 million people worldwide are affected by this disorder, making depression the leading cause of disability. Despite the widespread use of antidepressants, mortality remains a concern; severe depression remains associated with an increased risk of suicide, and depression after a myocardial infarction confers an increased risk of death.<sup>2,3</sup>

The categories of depression include major depressive disorder, premenstrual dysphoric disorder, dysthymic disorder, and unspecified depressive disorder. Although each diagnosis has distinguishing symptoms, all share the presence of a significant sad or irritable mood that impairs functioning and generally is associated with somatic or cognitive changes. The diagnostic criteria distinguish severity of symptoms on a scale from mild to severe.<sup>4</sup> Understanding that “depression” encompasses a wide range of disorders and that even major depressive disorder symptoms occur on a scale or gradation of severity is useful in devising appropriate treatment plans and strategies.

There are more than 24 FDA-approved antidepressants. All have the potential for side effects that may limit use, including weight gain, loss of libido, fatigue, and/or insomnia. Most take four to six weeks to demonstrate an effect.<sup>5</sup> A 2016 Canadian meta-analysis found about 50% of patients treated with a standard selective serotonin reuptake inhibitor (SSRI) failed or only partially responded to a first trial of antidepressants, and that the

literature lacks guidelines regarding second-line treatment. Often, when faced with a response failure, providers recommend a switch to another agent or augmentation with another medication — a slippery slope that can result in more side effects and complications from polypharmacy.<sup>6</sup>

The side effects from antidepressants, the need to wait at least a month before symptom relief, as well as the uncertainty of response and the possibility of needing to change agents to find the “one that works” lead many to look toward integrative health interventions.<sup>7</sup>

## BACKGROUND AND ORIGINS

Saffron, from the dried stigma of the delicate *Crocus sativus* plant, holds a special place in Greek mythology, attesting to the importance of this spice even in ancient times. According to the early Greeks, the young Spartan Krokus fell in love with a nymph, Smilax. Impressing the gods with his love and devotion, he was granted immortality by transforming into a plant bearing his name and symbol of his love — a blood red stigma. In another version, Krokus, distracted by his love while playing discus with Hermes (son of Zeus), is killed accidentally. The flower is again a symbol of his immortality, with the red symbolizing the spill of his blood.<sup>8</sup>

Although the myths of origin are subject to interpretation, the importance and use of saffron over time is more clearly documented. Between 3500-5000 B.C., the Sumerians used saffron gathered from the wild as a remedy and potion for a variety of ailments. It was in or near ancient Persia that cultivation of this prized plant began, most likely selecting flowers with longer stigma to increase yield of the saffron spice. Persian history

reveals saffron was mixed into hot tea to cure “melancholia,” and later Alexander the Great used saffron baths for generalized healing of wounds.<sup>9</sup>

Relics from the ancient Greek island of Santorini depict saffron production and application as a healing tool in pictorial form as early as 1700 B.C.<sup>10</sup> Although the ancient Greeks and Romans valued saffron for a variety of uses, including as a coloring agent, food additive, and perfume, Cleopatra of Egypt apparently thought saffron contributed to “more pleasurable lovemaking” and Pliny the elder recommended saffron in gastrointestinal disorders. As the uses of saffron broadened, so did its value, and trade of this precious spice across the Mediterranean boomed.<sup>9</sup>

Saffron found its way via trade routes into India and China by the early centuries A.D., and the plant began being cultivated in Kashmir. Uses in this region included medicinal applications for “melancholia” and inflammation, as well as numerous non-medicinal uses.<sup>9</sup>

In the first century A.D., Greek medical practitioner Pedanius Dioscorides compiled the *Materia Medica*, a reference book regarding botanicals in medical practice that documented the use of saffron for healing wounds and inflammation. Over subsequent years, use, demand, and production waxed and waned. The difficulty of cultivating and the painstaking manner of collection (still a factor today) affected use. The Black Death in the 1300s led to an escalation in demand and use of saffron in Europe to treat the victims. Ultimately, the 14-week long “saffron war” was fought after the theft of a shipment of saffron was hijacked by nobles intent on market domination and was followed by a period of high demand for the crop accompanied by piracy and diversion of the shipments.<sup>11</sup>

The use and value of saffron again varied over the next several centuries as it was first cultivated in western Europe but then attacked by fungus and disease. German settlers known as the Pennsylvania Dutch carried corms of the *Crocus sativus* plant to their new land and cultivated this crop in eastern Pennsylvania, where it remains grown today. However, the bulk of saffron worldwide continues to come from Iran (where it bears the nickname “red gold”) and Greece.<sup>9,11</sup>

#### PRODUCTION AND CHEMISTRY

Currently, saffron retails at up to \$11,000 per kilogram. This high cost is primarily because of the labor-intensive production, which requires 450,000 handpicked stigmas (from approximately 150,000 crocus blossoms) to produce one kilogram of saffron. These valuable stigmas contain four bioactive compounds of medicinal relevance and are rich in carotenoids, containing both lycopene and beta-carotenes.<sup>11,12</sup>

The major bioactive components of saffron are crocins and crocetin, responsible for the characteristic deep yellow color of safranin; picrocrocin, responsible for the characteristic bitter taste; and safranin responsible for the hay-like aroma. It is believed these compounds provide antidepressant benefits via several mechanisms, most of which primarily have been tested in vitro or in animals. The need for human testing remains a priority.<sup>11,12</sup>

**Antioxidant effect.**<sup>11,12</sup> Crocin, crocetin, and safranin are all strong antioxidants and may fight depression via protecting against and/or ameliorating oxidative stress (known to be increased in depression). Studies have shown that there is a synergistic effect when all three are present, enhancing potency under these conditions.

**Anti-inflammatory actions.**<sup>11,12</sup> Depression is associated with increased C-reactive protein, and inflammation is suspected to be a factor in this disorder. Saffron has been shown to have strong anti-inflammatory properties in the lab, most likely from crocin and crocetin, although further studies are necessary to elicit a mechanism of action.

**Serotonergic effect.**<sup>11,12</sup> SSRIs, such as fluoxetine, are a conventional treatment for depression. Crocins may have a similar effect with antagonistic action at serotonin receptor sites. Studies are ongoing regarding the use of saffron in premenstrual dysphoric disorder with this action as a postulated mechanism.

**Hypothalamus-pituitary-adrenal (HPA) modification.**<sup>11,12</sup> HPA dysregulation also has been investigated extensively in depressive disorders and is thought to affect neurotransmitter availability, oxidative stress, and inflammation. Saffron may lower the HPA response to stressful situations, but investigations are still in preliminary stages.

**Neuroprotection.**<sup>12</sup> Preliminary studies have looked at the neuroprotective effect of crocin and safranin in stressed rats. It is known that many of the conventional antidepressants increase brain-derived neurotrophic factor (BDNF), a brain protein thought to play a role in depression. Some researchers who have studied saffron and crocin have found similar effect on BDNF in rats exposed to stressful conditions.

#### CLINICAL STUDIES OF SAFFRON IN DEPRESSION

Two recent meta-analyses (2014 and 2015) included six high-quality, randomized, clinical trials regarding saffron and depression. Two hundred thirty adult patients participated in these studies. All were Iranian studies, all used the Hamilton Depression Rating Scale to measure outcome, and all were time-limited with a maximum of eight weeks until study conclusion. The intervention was a dose of 15 mg of standardized extract of saffron twice daily. Two studies were placebo-controlled, and four

studies compared efficacy to antidepressants (fluoxetine 20 mg or imipramine 100 mg daily.)<sup>12,13</sup>

All the studies included non-hospitalized subjects who met criteria for mild to moderate major depressive disorder with limited comorbidities. Extract sources were both from the petal of the flower and the stigmata, but interestingly showed no variation in efficacy. Large treatment effects were recorded for saffron compared to placebo, and no significant difference in improvement was noted in the studies looking at saffron vs. antidepressants; both interventions looked equally effective. (See Table 1.)

In even more recent studies, this trend of efficacy of saffron in treatment of depression continues. A 2016 12-week, placebo-controlled study by Mazidi et al included 60 adult patients and used a slightly higher dose of saffron at 50 mg daily. Significant lowering of depression as measured by the Beck Depression Inventory (BDI) was noted.<sup>14</sup> Talaie et al looked specifically at crocin (15 mg twice daily) as an adjunctive treatment to an SSRI in 40 patients and found statistically significant score improvement on the BDI after four weeks when compared with placebo.<sup>15</sup> A 2017 study by Kashani et al compared saffron (15 mg twice daily) to fluoxetine in the treatment of postpartum depression over six weeks; although the number of participants was low, the results suggested equal efficacy of the two agents.<sup>16</sup>

#### SAFETY

Safety and side effects of saffron clearly are an area for further study and methodical investigation. In all reviewed studies, saffron demonstrated side effects, including increased anxiety, increased appetite, nausea, and headache, although to varying degrees. In general, side effects from conventional antidepressants were less tolerated than side effects from the saffron or crocin groups; however, there was no clear statistical difference in adverse effects reported by any one group (including placebo).<sup>12,13</sup> In addition, there may be changes in serotonin levels in the brain, such that extreme caution is advised with co-use with pharmaceutical antidepressants that may have the same, or similar, mechanisms of action, especially due to the risk of serotonin syndrome.<sup>13</sup>

Toxicology reports are inconsistent, but some studies of saffron have shown mild prolongation of blood coagulation and platelet aggregation, leading to a cautionary note to those on anticoagulant medications or with a bleeding disorder.<sup>11,12,13</sup>

Safe doses are up to 1.5 g daily, while doses in excess of 5 grams daily may be toxic. Notably, doses for treatment of depression range from 30-50 mg daily, leaving a wide margin of error. However, it is useful to understand the potential of toxicity or even fatality (20 grams) when treating depression because of the potential for suicidal thinking.<sup>12,13</sup> As no published study of saffron has lasted

longer than 12 weeks, it is difficult to document any long-term safety concerns.

#### FURTHER DISCUSSION

A 2010 survey reported that close to half of all U.S. visits to integrative medicine providers involved a psychiatric problem; another survey reported that half of all U.S. adults with self-reported depression acknowledged using integrative therapies.<sup>7</sup> If only for these reasons alone, it is useful for the integrative provider to be prepared to discuss the use of saffron in treatment of depression. It is also relevant to note that studies of cognitive behavioral therapy in mild to moderate depression have shown results on par with conventional antidepressants and with the studies of saffron.<sup>17,18</sup> The American Psychiatric Association guidelines on treatment of depression encourage the use of psychotherapy as a first-line treatment in mild to moderate depression, while acknowledging that appropriate providers and patient preference is important to this decision and may sway the pendulum toward psychopharmacology, psychotherapy, or perhaps (optimally) a combination of the two modalities.<sup>19</sup>

It is equally important to understand the distinction between types of depression prior to making recommendations; patients with mild-moderate major depressive episodes have few symptoms in excess of those needed to qualify for a diagnosis and functional impairment is limited. The saffron studies excluded patients with more severe types of depression, hospitalized patients, and most comorbidities. For now, it is best to treat patients with severe depression, repeated episodes, and significant comorbidities with conventional antidepressants and appropriate psychotherapy.<sup>19</sup>

The scientific literature says little about the price of saffron supplements. Although bulk quantities are expensive, treatment doses are small enough that affordability may be within the reach of most. A 2013 review study noted an unwanted side effect of the rise in popularity of saffron may be an increase in attempts to adulterate saffron products.<sup>20</sup> Checking labels carefully and obtaining products from established and reliable sources remains a good rule for most supplements and certainly for saffron.

Remembering these caveats, the saffron studies in depression overall are compelling and persuasive. Clearly, we need studies with more subjects over a longer time and with standardized procedures and extracts. Such studies can answer questions such as the length of time needed to solidify treatment, the risks of long-term side effects, and processes to determine quality of a saffron capsule. It seems appropriate and potentially exciting to tell patients that early studies of 15 mg saffron capsules twice daily appear promising in adults and as effective (but not more effective) than antidepressants alone. Reviewing the safety information and the limited information regarding long-term use is necessary as well. As with all

**Table 1: Compilation of Clinical Trials on the Use of Saffron in Depression**

Author and Year	Type of Study and Number of Subjects	Dose of intervention	Scale Used to Measure Outcome	Study Arms	Result Summary
Hausenblaus et al. 2015 <sup>13</sup>	Six studies randomized, double-blind regarding depression  230 adult participants with major depressive disorder	Saffron capsule 30 mg/day	HDRS	Two studies: saffron vs. placebo  Three studies: saffron vs. fluoxetine  One study: saffron vs. imipramine	Statistically significant reduction in HDRS with saffron  Significant reduction in HDRS for all groups without statistically significant difference between groups
Talaei et al. 2015 <sup>15</sup>	Randomized, double-blind, placebo-controlled  40 adult patients with major depressive disorder	Crocin tablet 15 mg BID as adjunct to SSRI	BDI	Crocin plus SSRI vs. placebo plus SSRI  4 weeks	Significant improvement on BDI scores for crocin group ( $P < 0.0001$ )
Mazidi et al. 2016 <sup>14</sup>	Randomized, double-blind, placebo-controlled  60 adult patients with major depressive disorder	Saffron capsule 50 mg daily	BDI	Saffron vs. placebo  12 weeks	Significant improvement in BDI scores for saffron group ( $P < 0.001$ )
Kashani et al. 2017 <sup>16</sup>	Randomized, double-blind  64 adult women with mild-moderate postpartum depression	Saffron capsule 30 mg	HDRS	Saffron  15 mg BID vs. fluoxetine 20 mg	Remission and partial response rates almost identical between the two groups  ( $P = 1.00$ )

SSRI: selective serotonin reuptake inhibitors; HDRS: Hamilton Depression Rating Scale; BDI: Beck's Depression Inventory

herbal medicines, caution is advised regarding quality of individual preparations.

## CONCLUSION

There is no doubt that current research points to the efficacy of saffron in treatment of adults with mild to moderate major depression and perhaps in other forms of depression as well, such as postpartum depression. There is potential for use of saffron as an adjunct to antidepressant treatment, or as first-line therapy, and potential to isolate bioactive components (such as crocin) to use for antidepressant effect. Unfortunately, what we do not know about saffron — including specific mechanisms of action, optimal length of treatment, long-term side effects, relative efficacy of type of extracts, and use in pediatric and geriatric populations — remains significant and a barrier to common use. In the postpartum, breastfeeding population, studies regarding safety for infants must be established before recommendation for use.

When treating adult patients with mild to moderate major depression, the integrative provider is on solid ground exploring saffron as an alternative to conventional antidepressants. Understanding that the research is in early stages and that many questions remain unanswered is an

essential part of this discussion. Informing patients that nonpharmacologic interventions, such as cognitive behavioral therapy, have demonstrated similar benefits can help a patient both put the saffron results into perspective and make an informed decision regarding treatment options.

Addressing depression aggressively and promptly is helpful in preventing the debilitating and deteriorating course of untreated depression. The knowledge that alternative interventions exist can help lift the web of negative thinking and despair that so often accompanies a person in the midst of a depressive episode. Reminding patients that there are different avenues to symptom relief introduces hope and optimism — two important factors in the treatment of most disease states and certainly of particular relevance in the treatment of depression. Whether saffron will live up to its past reputation in healthcare remains uncertain, but the potential for use of this exotic spice in the treatment of depression is clear. ■

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## LOW BACK PAIN

### ABSTRACT AND COMMENTARY

# Yoga for Lumbago?

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**SYNOPSIS:** A review of randomized, controlled trials of treatments for chronic non-specific, low back pain revealed that yoga provides improvements in back-related function compared to non-exercise controls at intermediate time points, and in pain scores in the short term. Also, yoga seems to be comparable to exercise interventions, although the quality of evidence was low enough to preclude us from knowing for sure.

**SOURCE:** Wieland LS, et al. Yoga treatment for chronic non-specific low back pain. *Cochrane Database Syst Rev* 2017;1:CD010671.

Low back pain is a worldwide problem that has a reported prevalence of up to 84%, with a chronic prevalence of an estimated 23% of the population.<sup>1</sup> The U.S. National Health Interview Survey estimated the three-month prevalence of low back pain as 26.4%.<sup>2</sup> Treatment often is aimed at pain relief and dysfunction resolution, because there is often no known anatomical or pathologic cause for the problem.

The American College of Physicians (ACP) recently issued its clinical guideline for noninvasive treatments for acute, subacute, and chronic low back pain,<sup>3</sup> listing yoga as a strongly recommended initial course of therapy for chronic low back pain. It noted that only low-quality evidence existed for Iyengar yoga to improve function and

pain, based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. Yoga has become a popular form of lifestyle and exercise in the United States. A 2016 survey found that the top five reasons for students starting the activity were for flexibility, stress relief, general fitness, overall health, and physical fitness. It was estimated that 36.7 million people participate in yoga in the United States, a 79% increase from the previous study in 2012. Seventy-two percent of participants were women and 34% of the survey participants were likely to try yoga in the coming year.<sup>4</sup>

Wieland et al looked to assess the effectiveness of yoga in treating chronic, non-specific low back pain, defined as lasting three months or more and having an unknown

## Summary Points

- Yoga as a medical therapy appears to offer improved functional outcomes compared to no exercise at six months.
- Yoga appears to offer improved pain relief compared to no exercise at the first month of engagement.
- Rigorous outcomes research protocols and trials are lacking in providing adequate data for conclusive analysis of yoga as a therapy for back pain dysfunction and pain.

metabolic or anatomic cause.<sup>5</sup> The authors analyzed the effect of yoga practice compared to no treatment, waiting list or minimal (education) intervention, another active treatment, or yoga plus intervention, where it could be compared to the intervention alone. The review focused on the effect of yoga therapy on low back pain and function, in addition to adverse events that occurred. The review was limited to trials with participants 18 years or older and chronic non-specific low back pain was defined as three months or more duration. Of interest, the trials included yoga plus a component of meditation or controlled breathing. They excluded trials that examined yoga meditation or lifestyle without the physical component or trials with the physical component alone.

The authors searched MEDLINE, CENTRAL and Embase as of March 2016. They extracted data from 12 parallel, randomized, controlled trials published in English and carried out in the United States, the United Kingdom, and India. The trials included 1,080 participants, the treatment periods varied from one to 24 weeks, and the study periods varied from one week to 12 months.

The variation in treatment and study times created a dilemma for adequate assessment. The authors created and adjusted data groups to reflect these differences among the research trials. Outcome measures were grouped into four term measures: short (four weeks), short-intermediate (three months), intermediate (six months), and long (one year). The individual trials did not use the same pain scales to assess outcomes, so the authors transformed each study pain scale to a 0 to 100 scale and summarized the outcome data using the mean difference (MD). Multiple scales also were reported in the trials for back-related function; efforts were made to extract data from the Roland-Morris Disability Scale and the Oswestry Disability Index.

The authors used the GRADE approach in providing their strength of evidence assessments. In the analysis of the 12 trials, the authors believed the studies all had high risk of bias because the participants, therapists, and assess-

sors were not blinded to treatment groups, and the outcomes were self-assessed. Therefore, all outcomes were downgraded to “moderate.” Some studies were very small and others had discrepancies between the methods and results section, downgrading them for risk of reporting bias. Four studies did not address class attendance, putting the trials at risk for compliance bias, while other studies did not address attrition rates clearly and had missing data. If other serious forms of bias were present, then the certainty of evidence was downgraded further.

In nine trials comparing yoga treatment to non-exercise controls in back-related function, there was low-certainty evidence that yoga was superior at 4-6 weeks (95% confidence interval [CI], -0.71 to -0.19), 3-4 months (95% CI, -0.66 to -0.14), and 12 months (95% CI, -0.46 to -0.14) and moderate-certainty evidence that yoga was superior at six months (95% CI, -0.66 to -0.22). The reasons given for downgrading certainty of evidence included risk of bias, heterogeneity, and imprecision in measurement. Degree of improvement analysis was made difficult by the varied trial protocols, subjective response, study size, and duration, such that representative improvement was noted in terms of the Oswestry Disability Index or the Roland-Morris Disability Questionnaire of Pain Disability Index and reported in Table 1.

Six trials were analyzed for pain improvement compared to non-exercise controls. Yoga did not meet the pre-defined criterion for “clinical importance” of pain change in any of the studies, although the change was noted as statistically significant. There was very-low-certainty evidence of pain change at 4-6 weeks (95% CI, -20.85 to -0.81), moderate-certainty evidence at 3-4 months (95% CI, -7.04 to -2.06), and low-certainty evidence at six months (95% CI, -13.37 to -2.25). There was very-low-certainty evidence for no statistically significant difference in pain at 12 months (95% CI, -14.5 to 3.7). Reasons for downgrading the certainty of evidence were similar to the functional analysis. (See Table 1.)

Four trials in the analysis compared yoga to exercise, finding very-low-certainty evidence of effect, and concluding that yoga provided little or no difference in back function at six weeks (95% CI, -0.41 to 0.37), three months (95% CI, -0.65 to 0.20), and six months (95% CI, -0.59 to 0.19). One study assessed the pain effect of yoga compared with exercise. Because there was very serious risk of bias and imprecision, the authors found very-low-certainty evidence for an effect of yoga on pain at one month (95% CI, -19.90 to -10.10) and seven months (95% CI, -25.48 to -15.31), although the reported difference in pain was statistically and clinically significant. (See Table 2.)

Adverse events were not reported consistently through the trials; there were increased adverse events in the yoga groups compared to the non-exercise controls, but they

**Table 1: Summary of Findings, Yoga Compared With No Exercise**

Outcomes	Studies/ Participants	Comparative Effect*	Certainty of Evidence	95% Confidence Interval
<b>Function</b>				
Short term (1 month)	5/256	1.80 U lower	Low	-0.71 to -0.19
Short-intermediate (3 months)	7/667	2.18 U lower	Low	-0.66 to -0.14
Intermediate (6 months)	6/630	2.15 U lower	Moderate	-0.66 to -0.22
Long (12 months)	2/365	1.36 U lower	Low	-0.46 to -0.14
<b>Pain</b>				
Short term	2/40	10.38 U lower	Very low	-20.85 to -0.81
Short-intermediate	5/458	4.55 U lower	Moderate	-7.04 to -2.06
Intermediate	4/414	7.81 U lower	Low	-13.37 to -2.25
Long	2/355	5.40 U lower	Very low	-14.5 to 3.7
<b>Adverse Events</b>	6/696		Moderate	
*Back-specific function: Oswestry Disability Index/Roland-Morris Disability Questionnaire – lower score means better function. Back-specific pain: Aberdeen Pain Scale or VAS (range 0-100) – lower scores mean less pain. Adapted from: Wieland LS, et al. Yoga treatment for chronic non-specific low back pain. <i>Cochrane Database Syst Rev</i> 2017;1:CD010671.				

**Table 2: Summary of Findings, Yoga Compared With Exercise**

Outcomes	Studies/ Participants	Comparative Effect*	Certainty of Evidence	95% Confidence Interval
<b>Function</b>				
Short term (6 weeks)	2/248	0.11 U lower	Very low	-0.41 to -0.37
Short-intermediate (3 months)	2/249	0.99 U lower	Very low	-0.65 to -0.20
Intermediate (6 months)	2/249	0.90 U lower	Very low	-0.59 to -0.19
<b>Pain</b>				
Short term (4 weeks)	1/54	15.00 U lower	Very low	-19.90 to -10.10
Intermediate (7 months)	1/54	20.450 U lower	Very low	-25.48 to -15.32
<b>Adverse Events</b>	3/314		Low	
*Back-specific function: Oswestry Disability Index/Roland-Morris Disability Questionnaire – lower score means better function. Back-specific pain: Aberdeen Pain Scale or VAS (range 0-100) – lower scores mean less pain. Adapted from: Wieland LS, et al. Yoga treatment for chronic non-specific low back pain. <i>Cochrane Database Syst Rev</i> 2017;1:CD010671.				

were similar to those that occurred with back-focused exercise. Adverse effects of yoga included fear of worsening the condition being treated, further back pain, disc herniation, and headache exacerbation.

#### ■ COMMENTARY

The word “yoga” comes from the Sanskrit language and can be interpreted to mean “to join” or “to unite.” Yoga is an ancient lifestyle form, involving physical and mental practices with the goal of developing and harmonizing the individual’s mind, body, and spirit. The practice embodies diet, posture, breathing, cleansing, and meditative disciplines to achieve this. The traditional practices have evolved and branched over the centuries, becoming commercialized into many styles of practice today. Most of the therapeutic research in the Cochrane Review used

the Hatha, Iyengar, and Viniyoga styles, emphasizing restorative practice rather than active aerobic activity. Wieland et al found that yoga is more effective than non-exercise controls for back-related functioning at an intermediate time frame and for pain in the short term. They acknowledged that additional high-quality research is needed to improve knowledge of the effectiveness of yoga practice on non-specific low back problems, including specific populations, quality-of-life outcomes, depression, and long-term follow-up. There were too few good-quality studies available to complete the authors’ initial goals, which included study of subpopulations.

Overall, they suggested that further studies should be of low-risk bias and should include further reporting of adverse outcomes. A major concern with the certainty

of evidence created in these trials was with performance and detection bias, as none of the studies were blinded and many of the results were from self-reported data gathering. It would be difficult to blind the participants from their activity, but the data-gathering aspect could be managed by blinded researchers, improving certainty of evidence of future work.

Saper et al published a study showing non-inferiority of yoga treatment to physical therapy for low back problems.<sup>6</sup> They devised a randomized trial with study staff, who were blinded to treatment arms, analyzing paper surveys that were collected at designated study intervals.

Improving study size, terms of study, and reporting consistency are certainly doable for now, but fully blinded studies will be difficult to devise and carry out given the nature of yoga treatment. It is difficult to blind participants to this treatment, since it is so familiar to many. Therefore, it will be difficult to provide conclusive outcomes data for assessment.

Yoga practice seems safe by current studies, and appears to provide measurable improvements in function and pain relief for a common dysfunction. The ACP has

strongly recommended nonpharmacologic treatment with yoga for chronic low back pain when compared to usual care and educational intervention.<sup>3</sup> They believed that there were fewer harms associated with this type of treatment, while the benefits were evident. Until further evidence tells us otherwise, yoga appears as a viable option for improving the pain and dysfunction associated with chronic nonspecific back pain and can be added to the possible roads to improved health for our patients. ■

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## CARDIOVASCULAR DISEASE

### ABSTRACT & COMMENTARY

# Prevalence of Coronary Atherosclerosis in Indigenous South American Tsimané

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

**SYNOPSIS:** Tsimané, a population living in the Bolivian Amazon, have the lowest prevalence of coronary artery disease among any population studied; individuals  $\geq 40$  years of age have mean low-density lipoprotein and high-density lipoprotein of 91 mg/dL and 39.5 mg/dL, respectively, despite a high inflammatory burden from parasites and pathogens.

**SOURCE:** Kaplan H, et al. Coronary atherosclerosis in indigenous South American Tsimané: A cross-sectional cohort study. *Lancet* 2017;389:1730-1739.

**C**ardiovascular disease (CVD) is the leading cause of death globally and in the United States, with nearly one in every three deaths attributable to CVD.<sup>1</sup> In 2013, of 54 million global deaths, 17.3 million were from CVD.<sup>2</sup> Total costs of CVD were approximately \$320 billion in 2011.<sup>3</sup> Coronary atherosclerosis is a disease with fixed risk factors, such as genetics/family history, and modifiable risk factors, including hypertension, lipid/cholesterol profile, cigarette smoking, abdominal obesity, hypertension, alcohol intake, diabetes, and physical inactivity.<sup>2</sup> Almost 50% of the coronary artery disease risk is

### Summary Points

- An 80-year-old Tsimané has the vascular age of an American in his mid-50s.
- Compared to an unselected U.S. population, the coronary atherosclerosis findings translate to a 28-year lag for Tsimané before reaching a coronary artery calcium score of 100.

reduced after adopting a heart-healthy lifestyle, even in the face of high genetic susceptibility to heart disease.<sup>4</sup> Industrialization has been associated positively with an increase in the prevalence of coronary artery disease. However, research on mummies observed that populations that lived prior to industrialization demonstrated peripheral atherosclerosis, confirmed by calcium deposits in arteries. In these populations, the hypothesis is that high levels of inflammation from infection and an abundance of risk factors led to the development of atherosclerosis.

Kaplan et al measured the CVD risk factors, inflammatory burden, and coronary artery calcium (CAC) scores in a contemporary pre-industrial population to determine the prevalence of atherosclerosis in the setting of a high infectious inflammatory burden. The study was carried out between July 2014 and September 2015 on Tsimané, a population from Bolivia living along a tributary of the Amazon river. Tsimané live a forager-horticultural village lifestyle in thatched roof huts in communities of 60 to 200 people. Tsimané diet consists of 72% unprocessed, complex carbohydrates and wild fruits, 14% fat and 14% protein from nuts and seeds, and wild game caught from hunting with bows and arrows or fishing with arrows, lines, or nets. The complex carbohydrates are from slash-and-burn horticulture growing corn, plantains, manioc/cassava, and rice. Hunting sessions last more than an eight-hour workday and cover more than 11.18 miles (23,600 steps). Tsimané spend an average of four to seven hours per day in physical activity, with < 10% of their waking time spent sedentary. In contrast, more than 50% of Western waking time is sedentary.

The Tsimané Health and Life History Project team and the HORUS study team joined together to analyze data of 705 Tsimané individuals out of a population of 16,000 from 85 villages. Prior census results identified 1,214 individuals to be approximately older than 40 years of age. A random number generator was used to select the studied communities. Community rather than individual random selection was used, because it was more culturally appropriate and individuals wouldn't feel singled out.

In this study, 416 of the 1,214 individuals were not in the randomly selected sample communities, and 67 people were not available for scanning for various reasons. The researchers scanned 731 individuals, and data were missing for 26 individuals. Complete data were available for 705 individuals, 72 of whom showed incidental TB findings and were referred to appropriate specialists.

The researchers obtained fasting morning blood draws, including lipids, apolipoprotein A and B, oxidized low-density lipoprotein (LDL), high-sensitivity C-reactive protein (hs-CRP), nine cytokines, erythrocyte sedimentation rate, white blood cell differential, and glucose.

Framingham risk scores also were calculated to estimate the 10-year cardiovascular risk of each individual. A 16 detector row scanner and a licensed radiological technician obtained single ECG gated scan under supervision of a cardiologist team.

CAC scores are a measure of the calcified plaque in the coronary arteries, providing proof of coronary artery disease. The CAC score measures approximately one-fifth of the total atherosclerosis burden, as the non-calcified plaque is not measured.<sup>5</sup> Non-calcified plaques currently are not measured in clinical practice, as the software is still under research investigation. In current clinical practice, obtaining CAC scores in low-risk individuals is not recommended.

Tsimané CAC scores (in broad age categories) representing a contemporary pre-industrial population were compared with contemporary industrial population-based studies in the United States (Multi Ethnic Study of Atherosclerosis, MESA). Tsimané CAC scores also were compared with populations from Germany (Heinz-Nixdorf Recall) and Japan. CAC scores are stratified as: 0, almost no risk; 1-99, low risk; 100-399, moderate risk; and > 400, high risk.

Multivariate, zero-inflated, negative binomial regression was used to assess the association between Tsimané CAC scores and coronary artery disease risk factors (while controlling for age and sex), and logistic regression was used to test for factors that inflate CAC absence.

Akaike's information criteria were used to assess the fit of the model used to approximate this unknown reality. Incident rate ratio was used to indicate the proportional change in risk for each of the dependent variables. A ratio < 1 indicated decreased risk while a ratio > 1 indicated increased risk.

Baseline participant characteristics showed an average age of 58.7 years. The participants were approximately half female and half male, with an average body mass index of 24.1 kg/m<sup>2</sup> and an average body fat of 22.1%. Average systolic blood pressure was 116/73.4 mmHg, with a mean resting heart rate of 65.9 beats per minute. Older people had slightly higher systolic blood pressures and resting heart rates. Total mean cholesterol was 150.81 mg/dL, high-density lipoprotein (HDL) was 38.67 mg/dL, LDL was 92.81 mg/dL, and triglycerides were 106.28 mg/dL. The average hs-CRP was 3.7 mg/L and erythrocyte sedimentation rate was 22 mm/h. The prevalence of coronary artery disease risk factors (hypertension, high cholesterol, elevated blood sugars, obesity, and smoking) was very low across all age groups.

There was a very low baseline of coronary atherosclerosis as measured by CAC scoring. Of the 705 individuals

with complete data, 596 had CAC scores of zero, 89 had CAC scores of < 100, 20 had scores of  $\geq$  100, and only one individual had a score > 400.

After 75 years of age, 65% (38 of 48) of Tsimané individuals did not have CAC and only 8% had moderately increased calcium scores. Although Tsimané men had slightly higher CAC scores than Tsimané women, Tsimané men still had lower CAC scores than Japanese women who, until now, had the lowest reported CAC scores. In stark contrast, only 14% of the U.S. MESA population did not have any coronary artery calcium, and more than 50% had CAC scores of at least 100 Agatston units.

Not surprisingly, in this study, younger age, female gender, and lower triglycerides were associated with lower CAC. Body fat and hs-CRP were associated with higher CAC scores, but higher monocyte counts were associated with lower CAC scores.

#### ■ COMMENTARY

In the United States, the American Heart Association, the National Cholesterol Education Program, and the American College of Cardiology recommend obtaining a CAC score for people in the intermediate risk category of the Framingham CVD risk prediction algorithm.<sup>6</sup> Obtaining a CAC score is considered to be most beneficial for patients in the intermediate risk category with undiagnosed chest symptoms and or equivocal results from other noninvasive testing and is not recommended for asymptomatic low-risk individuals.<sup>6</sup> The CAC score can be transformed into arterial age at which the individual's CVD risk is equal to that of the observed CAC score.<sup>7</sup> It is alarming that an 80-year-old Tsimané is the vascular equivalent of a 50-year-old American.

National Lipid Association guidelines and National Cholesterol Education Program guidelines are similar for cholesterol in low-risk individuals, where LDL-c of < 100 mg/dL is considered desirable.<sup>8,9</sup> The average LDL-c in Tsimané would meet both these recommendations. However, perhaps the recommendation for a total cholesterol of < 200 mg/dL in low-risk individuals should be lowered further to < 160 mg/dL to achieve an even lower prevalence of coronary artery disease as seen in Tsimané.

In other cross-sectional studies of contemporary pre-industrial societies, such as Kalahari bushmen, Tarahumara, rural Chinese, and Okinawans who consume a primarily plant-based diet, very low rates of CVD were noted.<sup>10</sup> Cholesterol levels are also lower. For example, in the Tarahumara, average total cholesterol is 136 mg/dL, and in populations from rural China, average total cholesterol is 127 mg/dL.<sup>10,11</sup> Dietary approximations of 13% protein, 75% carbohydrates, and 12% fats in the Tarahumara<sup>11</sup> are similar to the percentages of Tsimané.

Interestingly, the same risk factors, such as younger age, female sex, lower triglycerides, and body fat, affect both Tsimané and the U.S. population. However, the degree to which the CAC worsened with age was moderated in Tsimané because of the lower incidence of risk factors. However, because of the low prevalence of CVD in Tsimané, the zero-inflated, negative, binomial model explained 19% of the outcome: CAC score. This model included age, sex, body fat, and hs-CRP and did not include diet and physical activity. Perhaps if it had included diet or physical activity, the percentage explaining the outcome could have been much higher. It would be interesting to analyze the MESA data similarly to compare the model predictions of CAC scores in a different society.

Despite the high inflammatory burden from pathogens and parasites, Tsimané still were protected against coronary artery disease. Interestingly, helminth infections were associated with lower CAC scores even though more than 90% of adults at cross-sectional sampling suffered from helminth infections. The most common helminth infections in Tsimané include hookworm, *Ascaris lumbricoides*, and *Giardia lamblia*. Earlier studies have suggested that helminths may protect against heart disease and type 2 diabetes because they decrease total cholesterol by using the host's cholesterol for their own use, lower blood glucose by consuming the host's glucose, and shift the inflammatory response toward a type 2 helper (TH2) cell response.<sup>12</sup> A TH2 response is characterized by high IL-10 (which is anti-inflammatory), IL-5 levels, and other interleukins. The data from Tsimané offer further evidence to suggest that the type of immune response activated by infection or autoimmune disease is key.

The authors acknowledged the key limitations of the study, such as using CAC without contrast as a direct measure of coronary atherosclerosis, which would preclude assessment of non-calcified plaque reconstruction. They also acknowledged the possibility of ecologic fallacy in which aggregate risk factors may not translate into individual risk factors. Further genetic analysis is still underway (M Gurven, PhD, personal communication, July 7, 2017). However, epidemiological data suggest that Tsimané may not have a genetic protective effect. This is reflected by slight increases, over the past 10 years, in biomarkers (increasing blood sugars, cholesterol, weight, and body fat) in relation to changes in the environment of increased sugar consumption and decreased physical activity. If Tsimané did have genetic protective effects such as those seen in people with PCSK9 mutations, their cholesterol levels would be more consistent despite the changing environment.

Not surprisingly, the individual with a CAC score > 400 had blood pressure 140/88 mmHg, CRP 4.11 mg/dL, body fat 36.6%, weight 65 kg, height 145 cm, LDL 183, HDL 30, and was a 69-year-old female from a more ac-

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cultured village (M Gurven, PhD, personal communication, July 7, 2017).

Overall, this was a very interesting cross-sectional study with a high percentage of community involvement — more than 50% of the community was sampled. The findings agreed with prior studies of populations having very low CVD prevalence, eating mostly plant-based diet, having low cholesterol, obtaining plenty of physical activity, abstaining from smoking, and having normal BMI, low blood pressure, and low blood glucose. ■

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## CME QUESTIONS

1. Which of the following is a potential benefit of saffron over conventional antidepressants in treatment of depression?
  - a. There are few, if any, side effects documented with saffron.
  - b. Saffron represents a viable alternative that may be encouraging and acceptable to many patients with depression, especially those looking for a natural or plant-derived medication.
  - c. There is no known toxicity for saffron.
  - d. Saffron demonstrated greater efficacy in treating depression than most antidepressants.
2. Which of the following statements is true regarding the recent review of yoga treatment for chronic non-specific low back pain?
  - a. There is moderate-certainty evidence that yoga therapy is superior to no exercise in improving low back function at one year.
  - b. There is low-certainty evidence that yoga therapy is superior to no exercise in improving low back pain at one month.
  - c. There is moderate-certainty evidence that yoga therapy is superior to no exercise in improving low back function at six months.
  - d. There is low-certainty evidence that yoga therapy is superior to no exercise in improving low back pain at three months.
3. Which of the following statements is true about research in the Tsimané population?
  - a. Tsimané men had a higher prevalence of coronary atherosclerosis than Japanese women, but similar prevalence to Japanese men.
  - b. Despite a high inflammatory burden, Tsimané have the lowest prevalence of coronary atherosclerosis of any population yet studied.
  - c. The higher the hs-CRP scores, the lower the coronary artery calcium score, all other factors being equal.
  - d. Age, male sex, body fat, hs-CRP, and high monocyte counts were associated with higher CAC scores.

## [IN FUTURE ISSUES]

Exercise and breast cancer risk

Omega-3 fatty acids for cardiovascular disease

Exercise and depression in children

Mind-body medicine: A review

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