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ESSENTIAL OILS

ABSTRACT & COMMENTARY

Peppermint Oil for IBS?

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Dr. Coutinho and Dr. Selfridge report no financial relationships relevant to this field of study.

SYNOPSIS: The PERSUADE study, a randomized, placebo-controlled trial of two formulations of peppermint oil, demonstrated no statistically significant reduction in abdominal pain response nor overall symptom relief in Rome IV IBS patients using Food and Drug Administration/European Medicines Agency endpoint criteria over an eight-week trial period.

SOURCE: Weerts ZZRM, et al. Efficacy and safety of peppermint oil in a randomized double-blind trial of patients with irritable bowel syndrome. *Gastroenterology* 2019; S0016-5085(19)41246-8. doi:10.1053/j.gastro.2019.08.026. [Epub ahead of print].

Irritable bowel syndrome (IBS), a high-prevalence (10-20%), complex, gut-brain functional disorder, is associated with a significant negative effect on patients' quality of life. Current pharmaceuticals include antispasmodics, laxatives, antidiarrheal agents, and antidepressants. None of these demonstrate high-level effectiveness for all symptoms and several have significant side effects, risks, or drawbacks, including cost.[1]

Historically, peppermint oil has been used in herbal pharmacopeia for treating digestive disorders, including dyspepsia and gallbladder disease. Meta-analyses of peppermint oil research have concluded that moderate evidence exists for the use of peppermint oil for IBS-related abdominal pain.[2] In fact, the Canadian Gastroenterology Association clinical practice algorithm for IBS treatment includes soluble fiber and peppermint oil as initial treatments for IBS defecation-related abdominal pain, before considering prescription medication.[3] Active ingredients in peppermint include menthol and other volatile oils that appear to relax smooth muscles through the antagonism of calcium channels in the gut.[2] The introduction of Rome IV Criteria for IBS diagnosis, as well as changes in Food and Drug Administration

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Integrative Medicine [ALERT]

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Summary Points

- Two peppermint oil formulations (a small intestinal-release product and an ileocolonic-release product) did not reduce abdominal pain response nor provide overall symptom relief compared to placebo.
- Small intestinal-release peppermint oil did significantly reduce abdominal pain, discomfort, and irritable bowel syndrome severity as secondary outcomes; ileocolonic-release peppermint oil demonstrated no significant symptom reduction.
- Adverse events related to peppermint oil were mild and transient, consisting mainly of heartburn and gastroesophageal reflux-type symptoms.

(FDA) and European Medicines Agency (EMA) defined IBS trial endpoints focused on reduction of IBS-associated abdominal pain, prompted the authors of this study to a re-evaluate the efficacy and safety of peppermint oil within these strict outcome parameters.[4,5]

The PERSUADE trial is a randomized, double-blind, placebo-controlled study, conducted in four secondary and tertiary hospital care centers in the Netherlands that evaluated peppermint oil for the management of IBS as defined by Rome IV criteria. (*See Table 1.*) The trial recruited 189 patients between the ages of 18 and 75 via primary care and hospital outpatient clinics, as well as self-referral through public advertising and social media. Eligible patients were those who met Rome IV criteria and averaged numerical rating scale (NRS) pain scores of at least three on an 11-point scale of 0-10 with "0" representing "no pain" and "10" representing "worst pain ever," over the course of a 14-day pretreatment period. Patients were randomized, using ALEA Screening and Enrollment Application Software, with respect to IBS type (constipation, diarrhea, or mixed), study center, age, and gender. Patients were placed within one of three treatment groups: small intestine-release peppermint oil, ileocolonic-release peppermint oil, and placebo. Treatment consisted of one self-administered capsule, containing 182 mg (0.2 mL) of peppermint oil, three times daily, 30 minutes before breakfast, lunch, and dinner over the course of eight weeks. All capsules were coated with an additional hard encapsulation of gelatin to ensure no peppermint scent or flavor interfered with blinding. Primary and secondary endpoints were measured weekly using NRS scales for pain and global symptom relief, as well as several other symptom and quality of life surveys, and results were recorded via electronic data capture.

The primary endpoint for determining efficacy of peppermint oil was strictly defined (according to the FDA) as a reduction in weekly average abdominal pain compared to baseline by at least 30% in at least 50% of the treatment period using the NRS 11-point pain survey, which was assessed daily. The co-primary endpoint, per EMA recommendations, was global relief of IBS symptoms on an NRS seven-point survey, in at least 50% of the weeks during the eight-week treatment period, assessed weekly.

Secondary endpoints defined efficacy of peppermint oil by less strict outcomes on the NRS 11- and seven-point instruments, and included a variety of online surveys assessing reduction in IBS symptom severity, symptomatic improvement of abdominal pain, abdominal discomfort, abdominal bloating, abdominal cramping, belching, nausea, defecation urgency, anxiety, and quality of life. Incidence, nature, and severity of adverse effects occurring during the treatment period were documented daily.

Sample sizes were estimated using data from a 2014 *Journal of Clinical Gastroenterology* meta-analysis adjusted for heterogeneity and the anticipated dropout rate.[6] All analyses were subject to the intention-to-treat principle. Per-protocol analyses were performed for data sets from patients who demonstrated 80% adherence to treatment and completed the treatment period. Because of multiple between-group comparisons, two-sided P values $\leq 0.04/5 = 0.0125$ were considered statistically significant for the primary outcomes. Secondary outcomes with $\alpha < 0.025$ were determined statistically significant.

Table 1. Rome IV Diagnostic Criteria for Irritable Bowel Syndrome

- Recurrent abdominal pain on average at least 1 day/week in the last three months, associated with two or more of the following:
  - Related to defecation
  - Associated with a change in stool frequency
  - Associated with a change in stool form (consistency)
- Criteria must be fulfilled for the last three months; symptom onset at least six months prior to diagnosis

There was no statistically significant difference in the reduction in the weekly average abdominal pain primary endpoint between peppermint oil treatment groups vs. placebo: 46.8% in small intestinal-release peppermint oil (odds ratio [OR] 1.68; 95% confidence interval [CI] [0.80, 3.51]; *P* = 0.170; number needed to treat [NNT] 8.1) and 41.3% in ileocolonic-release peppermint oil (OR 1.39; 95% CI [0.66, 2.90]; *P* = 0.385; NNT 14.5), compared with 34.4% in placebo. (*See Table 2.*) There was no statistically significant difference in the co-primary outcome of global relief of IBS symptoms between treatment groups and placebo: 9.7% in small intestinal-release peppermint oil (OR 2.12; 95% CI [0.49, 9.17]; *P* = 0.317), and 1.6% in ileocolonic-release peppermint oil (OR 0.33; 95% CI [0.03, 3.35]; *P* = 0.351), compared with 4.7% in placebo. (*See Table 2.*)

Noteworthy findings outside the strictly defined primary and co-primary endpoints were reported. During week 8, for example, patients receiving small intestinal-release peppermint oil had a significantly greater reduction in abdominal pain, with a corrected difference in change from baseline on the 11-point NRS, compared with placebo, of -0.63 (95% CI [-1.14, -0.12]; *P* = 0.016). Patients receiving small intestinal-release peppermint oil also experienced reduction in the secondary outcome of abdominal discomfort. Corrected differences in change from baseline on the 11-point NRS were significant during week 6 (-0.95; 95% CI [-1.74, -0.15]; *P* = 0.020) and week 7 (-0.97; 95% CI [-1.71, -0.24]; *P* = 0.009) of treatment. The secondary outcome of IBS symptom severity was improved in patients receiving small intestinal-release peppermint oil, with a corrected difference in change from baseline of 41.8 on the IBS Symptom Severity Score total score. An improvement of -91.5 for small intestinal-release peppermint vs. -49.8 for placebo was seen during week 8 of treatment (95% CI for difference [-76.88, -6.70]; *P* = 0.020).

Adverse effects, such as heartburn, belching, and headache, were more prevalent in both groups of patients receiving peppermint oil. Reported mean for side effects was 4.26 (0.37) for small intestinal-release (*P* = 0.012) and 4.54 (0.45) for ileocolonic-release peppermint oil (*P* = 0.001) compared with 2.78 (0.34) for placebo.

■ COMMENTARY

This is the first high-quality randomized, double-blinded, placebo-controlled investigation of peppermint oil for relieving IBS symptoms. This accomplishment alone is commendable. Although this IBS interventional study concludes that peppermint oil does not improve IBS pain and global symptoms, it does so using the FDA and EMA outcome endpoints for the NRS 11 and NRS 7 instruments, respectively. The authors admit that these stringent outcome endpoints may not reasonably reflect clinical response given the wide range of symptoms commonly suffered by IBS patients and the perceived impact on quality of life. In fact, pain and global symptom improvement with small intestinal-release peppermint oil did reach statistical significance in this study, when lower NRS 11 and NRS 7 thresholds were used and additional secondary outcome measures of symptom improvement and quality of life were applied. These latter findings are consistent with the results of recent meta-analyses indicating a beneficial effect of peppermint oil for IBS symptoms.[6-8] Further, adverse events related to both peppermint oil formulations were mild and transient, and consisted mostly of self-limited heartburn and gastroesophageal reflux disease symptoms, likely related to the proven relaxing effects of the menthol component of the oil in the lower esophageal sphincter. When compared to placebo-controlled studies evaluating several newer IBS drugs (linaclotide, plecanatide, eluxadoline), small intestinal-release peppermint oil performed similarly in this study in terms of NNT. All pharmaceutical agents currently marketed to treat IBS have significantly less favorable adverse event profiles. Peppermint oil is inexpensive compared to pharmaceuticals, as well. A 30-day supply (enough for three doses per day) of 0.2 mL enteric coated peppermint oil capsules can be purchased from a popular online marketplace vendor for approximately $12.

One aim of the authors of this study was to evaluate an ileocolonic-release peppermint oil formulation, based upon the hypothesis that a more local anti-nociceptive effect on colonic sensory afferent receptors would demonstrate superior effectiveness. This was not the case and the authors concluded that further pursuit of this novel formulation as an IBS intervention is not indicated. Because of the low cost, mild and transient side effect profile, and demonstrated moderate efficacy for IBS symptoms supported by this well-constructed study, peppermint oil remains an appropriate treatment in initial IBS defecation-related abdominal pain symptom management for patients who prefer a non-pharmaceutical, plant-based option. ■

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Table 2. Peppermint Oil Effect on Irritable Bowel Syndrome Symptoms

	Placebo n = 64	Small Intestinal-Release Peppermint Oil n = 62	Ileocolonic-Release Peppermint Oil n = 63
	# Responders (%)	# Responders (%); *P* value; Odds Ratio (95% CI)	# Responders (%); *P* value; Odds Ratio (95% CI)
Primary Endpoints			
Abdominal Pain, 30%*	22 (34.4)	29 (46.8); *P* = 0.170; 1.68 (0.80-3.51)	26 (41.3); *P* = 0.385; 1.39 (0.66-2.90)
Global relief**	3 (4.7)	6 (9.7); *P* = 0.317; 2.12 (0.49-9.17)	1 (1.6); *P* = 0.351; 0.33 (0.03-3.35)
Secondary Endpoints			
Moderate relief†	13 (20.3)	24 (38.7); *P* = 0.030; 2.47 (1.09-5.56)	13 (20.6); *P* = 0.980; 0.99 (0.41-2.38)
Abdominal Pain, 50%††	8 (12.5)	16 (25.8); *P* = 0.062; 2.51 (0.96-6.59)	13 (20.6); *P* = 0.220; 1.85 (0.69-4.96)

*At least 30% reduction in mean worst abdominal pain in at least 4 out of 8 weeks (Food and Drug Administration recommendation)
**A global relief score of at least 6 or 7 (on a 7-point NRS) in at least 4 out of 8 weeks (European Medicines Agency recommendation)
†A global relief score of at least 5, 6, or 7 (on a 7-point NRS) in at least 4 out of 8 weeks
††At least 50% decrease in mean worst daily abdominal pain in at least 4 out of 8 weeks
CI: confidence interval

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AROMATHERAPY

ABSTRACT & COMMENTARY

Lavender Aromatherapy During Chemotherapy

By David Kiefer, MD, Editor

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SYNOPSIS: Lavender oil aromatherapy demonstrated some benefits in sleep and anxiety for people undergoing chemotherapy.

SOURCE: Özkaraman A, et al. The effect of lavender on anxiety and sleep quality in patients treated with chemotherapy. *Clin J Oncology Nursing* 2018;22:203-210.

In the search for the safe and effective use of essential oils, there is some guidance in the medical literature. Most of the human studies have explored the use of essential oils in aromatherapy, and this clinical trial is no exception. The authors chose lavender oil (*Lavandula angustifolia*, Family Lamiaceae, flowers) aromatherapy for this intervention, due to the known GABA-nergic, and hence relaxing, effects of lavender, which has been well-supported by numerous prior clinical trials.[1-4] Interestingly, one of the studies[1] was in a similar demographic as the current clinical trial, namely, the use of lavender aromatherapy in people undergoing treatment for cancer. The authors, through a thorough literature review in their introduction, make a compelling case for the need for anti-anxiety and sleep-promoting treatments during cancer therapeutics.

The study took place in Turkey; although not expressly stated as such, all of the authors work at universities in Turkey. The researchers recruited adults with cancer who were about to receive their first series of outpatient, weekly chemotherapy treatments with paclitaxel (other chemotherapeutic agents also could be used). The recruits had to have a sense of smell to be included. The type of cancer was variable (but mostly breast cancer) as mentioned in their demographics table, though the staging was not detailed. People were excluded from the study if they had a chronic disease (cardiovascular disease and asthma were singled out) or a psychiatric diagnosis (including anxiety), were taking a medicine for anxiety, or if they had a "known history of allergy." It is unclear if that meant a known history of allergy to lavender.

The participants were randomized to either aromatherapy with lavender (n = 30) or tea tree oil (n = 20) (in bottles with numbered labels), or a control group (n = 20) who received no aromatherapy. Both the patient and the administering nurse were blind to the treatment bottles, which arguably was compromised as soon as the bottles were opened. The researchers purchased the two essential oils from the same reputable and quality-controlled company; they chose tea tree oil as a placebo due to the lack of sedative properties. For the intervention, three drops of the oil were placed on a cotton ball that was set 10 inches below the nose near the neck and shoulders during each chemotherapy treatment of the "first cycle," which presumably referred to a series of treatments but was not specified by the authors. In addition, for one month after the cessation of chemotherapy, participants were instructed to smell the oil for five minutes at 9 p.m. It was unclear whether cotton balls were used again or the participants simply opened the bottled and inhaled.

The researchers collected demographic data from the participants, and then measured anxiety and sleep with the State-Trait Anxiety Inventory (STAI; in two parts, S-Anxiety and T-Anxiety) and Pittsburgh Sleep Quality Index (PSQI), respectively, as per Table 1. Just before the first chemotherapy treatment and after completion of chemotherapy, all three of the tests (S-Anxiety, T-Anxiety, and PSQI) were administered. There is some confusion in the text about when the second testing occurred; that information likely was collected one month after the last chemotherapy treatment, after one month of nightly home aromatherapy treatments.

Summary Points

- Seventy people with cancer and pending chemotherapy were randomized to aromatherapy with lavender oil, tea tree oil, or neither (the control group).
- Surveys exploring anxiety and sleep were given to the participants at baseline and after completing chemotherapy and, in the intervention groups, one month of nightly home aromatherapy treatments.
- There were no benefits in short-term anxiety, but lavender oil aromatherapy benefited chronic anxiety and sleep over the treatment period more than the control group or tea tree oil aromatherapy.

Table 1. Anxiety and Sleep Surveys

Name	Subset (if applicable)	Scale	Comments
State-Trait Anxiety Inventory (STAI)	S-Anxiety (State)	1 (never) – 4 (always) for 20 short statements (80 points possible)	Focuses more on temporary anxiety
State-Trait Anxiety Inventory (STAI)	T-Anxiety (Trait)	1 (never) – 4 (always) for 20 short statements (80 points possible)	Focuses more on chronic anxiety
Pittsburgh Sleep Quality Index (PSQI)	N/A	Open-ended and multiple-choice questions; answers range from 0-3 for 7 components (21 points possible)	Lower scores indicate better sleep

Table 2. Survey Results for Baseline and Post-Chemotherapy

Group	S-Anxiety	T-Anxiety	PSQI
Lavender: baseline	41.4	44.8	7.6
Lavender: post-chemo	42.4	**40.8**	**3.9**
Tea tree: baseline	45.3	45.4	9.2
Tea tree: post-chemo	45.3	45.2	**5.9**
Control: baseline	42.0	45.4	7.05
Control: post-chemo	42.4	45.25	7.15

S-Anxiety and T-Anxiety from the State-Trait Anxiety Inventory.
PSQI: Pittsburgh Sleep Quality Index
The three primary significant differences (variable *P* values) are in bold.

The authors mention that the study participants were "homogenously distributed across groups," and this appears to be supported by a demographic table that shows similarities in age (median 57-58), gender (more females than males), education (mostly primary school), marital status (majority married), and income.

Outcome results are shown in Table 2. For S-Anxiety, there was no change from the first to the second assessment for any of the groups, nor was the level of anxiety different between the groups. For T-Anxiety, the authors state similarities between the groups at baseline, but an improvement ($P = 0.003$) between the time points, and a statistically significant intergroup difference ($P < 0.001$). Looking at the numbers in the table, this conclusion seems unlikely, so one doubts the validity of their statistics. They do describe that most of the time difference stems from the lavender group (44.8 improving to 40.8) and the intergroup difference is due to the lavender post-chemotherapy (40.8) vs. the tea tree post-chemotherapy (45.2). For PSQI, both the lavender and tea tree aromatherapy groups improved over time ($P < 0.001$), but the control group did not. The authors state a significant intergroup difference, but it is unclear what that refers to; the only clarifying prose conveyed is that the second assessment for lavender was different than the second assessment for the control group.

Of note, no details were provided for adverse effects or participants who may have dropped out of the study.

■ COMMENTARY

Methodologically, this study was less than ideal. However, if we look past those flaws, there may be some clinical insight relevant to treating people with anxiety and insomnia as they progress through chemotherapy and afterwards. In order to accept these results, we are assuming that no participants dropped out of the study, took any sleeping medicine (anti-anxiety medicines were prohibited), and adhered to the nightly aromatherapy treatments (unless they were in the control group). If this is the case, then there was a benefit of lavender oil aromatherapy in trait (or long-term) anxiety and sleep. The lavender anxiety effects were above-and-beyond benefits seen with tea tree oil aromatherapy and the control group, whereas the lavender sleep effects were only statistically significant when compared to the control group. This is notable, and potentially a useful adjunctive therapy for a demographic already facing treatment challenges through cancer therapy.

If we add a follow-up study to our wish list for anxiety and insomnia treatment options, it might be useful to review the flaws in this clinical trial. Perhaps the next set of researchers will keep these in mind in future study designs. For this study, the description was a little difficult to follow. Some basic tenets of a clinical trial publication were lacking, such as the actual process of recruitment, specifics of diagnosis, and corroboration at study conclusion that patients did not know which group they were assigned to (which is difficult given the olfactory clues from essential oils). Such unblinding certainly could have affected the final results. In fact, this might explain why there was a response in the sleep survey to the tea tree oil group; there should not have been any improvement in sleep, since tea tree oil does not have anti-anxiety or other relaxing effects. Perhaps the ritual of going through an aromatherapy explains some of the benefits seen, which was lacking in a control group with participants who did not have that ritual. Another question about the methodology is that why, if randomization was used, was there such a disparity in numbers in each of the groups? In addition, the exact method for administration of the aromatherapy at home was not described. All of this information is necessary to apply these results in clinical practice or to consider replicating the study in a follow-up clinical trial. Finally, as we ponder the potential benefits of the treatment intervention, it is imperative to know whether there were any observed adverse effects or plant-pharmaceutical interactions. For example, the author of this review can attest to at least one patient in his panel who has an allergic reaction to lavender, even in aromatherapy form.

Assuming a favorable safety profile, for patients going through chemotherapy, especially those with insomnia or chronic anxiety, it certainly can be worth considering lavender aromatherapy if it is permitted in the clinic or hospital setting, and if the patient would agree to home treatments after cessation of chemotherapy. The ritual and the physiological effects may indeed combine to benefit pre-existing anxiety or sub-standard sleep and contribute to overall health through the cancer treatment process. ■

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VEGETARIANISM

SHORT REPORT

Vegetarians and Stroke

By Eric Neilson, MD

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

SYNOPSIS: A prospective cohort study in the United Kingdom demonstrated that vegetarians have a 22% lower incidence of ischemic heart disease, but a 20% increased incidence of total stroke, mostly related to hemorrhagic stroke, when compared to meat eaters. No difference in ischemic stroke or acute myocardial infarction was found.

SOURCE: Tong TYN, et al. Risks of ischaemic heart disease and stroke in meat eaters, fish eaters, and vegetarians over 18 years of follow-up: Results from the prospective EPIC-Oxford study. *BMJ* 2019;366:l4897.

Published dietary recommendations are often confusing, controversial, or contradictory. This is especially true for vegetarian diets and red meat consumption, wherein current recommendations vary widely. The *Annals of Internal Medicine* recently published, with low-certainty evidence, a weak recommendation for adults to continue current processed and unprocessed red meat consumption.[1] The World Health Organization's International Agency for Research on Cancer lists processed meat in the Group 1, carcinogenic to humans, classification.[2] American College of Cardiology (ACC)/American Heart Association (AHA) guidelines strongly recommend (Class I, Level A evidence) a diet high in vegetables, fruits, and whole grains, including low-fat dairy, poultry, and fish, with limited red meat.[3] Providing patients with clear, unambiguous dietary advice seems to be an impossible mission. Tong et al in *BMJ* offer evidence that further complicates this conversation. These authors followed nearly 50,000 vegetarians, red meat eaters, and pescatarians over the course of 18 years to monitor stroke and ischemic heart disease outcomes.

Using proportional hazards regression models for associations between diet groups, results indicated that compared to a diet inclusive of red meat, a pescatarian or vegetarian diet is associated with a decreased risk of ischemic heart disease. However, when compared to a diet including red meat, a vegetarian diet is associated with increased risk of total and hemorrhagic stroke. This risk reduction translates to four and 10 fewer incidents of ischemic heart disease per 1,000 persons over 10 years for pescatarians and vegetarians, respectively, compared to red meat eaters (predicted incidents per 1,000 population: 40.4 pescatarians and 36.2 vegetarians vs. 46.2 meat eaters; 95% confidence interval [CI] and *P* heterogeneity value < 0.001). Vegetarians had three more cases of total stoke per 1,000 persons over 10 years compared to red meat eaters (18.3 vs. 15.4; 95% CI and *P* heterogeneity value = 0.04). Data indicated that there was no statistically significant increase in stroke incidence for pescatarians. Continued research on larger and more diverse groups of participants and considerations of the effects of specific nutrients associated with variations in diet (e.g., cholesterol, fatty acids, vitamin B12), are critical to determine the underlying mechanisms for the results found in this study. This nutritional study also is complicated by self-reporting, exclusion of high calorie intake, and changes in diet over time, which must be a component in future research. The study supports general ACC/AHA guidelines and indicates the need for physicians to have discussions with patients regarding the risks and benefits of individual dietary considerations. ■

Summary Point

- Vegetarian and pescatarian diets are associated with a decreased incidence of ischemic heart disease; however, vegetarians have higher rates of hemorrhagic and total stroke.

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SHORT REPORT

Soft Drinks and Death

By Ellen Feldman, MD

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

SOURCE: Mullee A, et al. Association between soft drink consumption and mortality in 10 European countries. *JAMA Intern Med* 2019. doi:10.1001/jamainternmed.2019.2478. [Epub ahead of print].

SYNOPSIS: This long-term, large-scale European study finds that higher use of total soft drinks is associated with a higher risk of death; additionally, higher use of artificially sweetened soft drinks is associated with higher risk of death from cardiovascular illness and higher use of sugar-sweetened soft drinks is associated with higher risk of death from digestive illnesses.

Are soft drinks bad for health? Results from observational studies based primarily in the United States suggest a link between all-cause mortality and higher consumption of both sugar and artificially sweetened beverages.[1,2] However, sugar-sweetened drinks remain the top contributor to added sugar in a typical American diet, with close to half of adults reporting daily consumption.[3]

Mullee et al present the results of a large-scale European study not only looking into all-cause mortality, but into specific cause as well. Drawing from eligible participants in the ongoing European Prospective Investigation into Cancer and Nutrition (EPIC), a 10-country, population-based, prospective investigation, 451,743 participants were tracked over a mean of 16.4 years. Dietary habits, specifically the rate of consumption of both artificially and sugar-sweetened soft drinks, were evaluated at entrance into the study. Specific causes of death were recorded. Collection of data varied depending on the country; in most cases, dietary assessment was conducted via self-administered questionnaires, although some locations used in-person interviews. Deaths were determined based on local registries or active inquiry.

In an effort to limit confounding conditions, participants with prior diagnoses of cancer, heart disease, stroke, and diabetes were excluded from this investigation population.

One glass of a soft drink was defined as approximately 250 mL. Higher risk of all-cause mortality was found in respondents drinking more than 125 mL daily of artificially sweetened soft drinks and more than 225 mL daily of sugar-sweetened soft drinks, with hazard ratios (HR) peaking above 1.2 with soft drink consumption above 900 mL daily.

Summary Point

- In a cohort of more than 400,000 people being followed by a multicenter, European study, increased risk for mortality (variable causes) was seen for soft drinks, both artificially and sugar-sweetened.

When the authors compared two or more glasses of soft drinks daily vs. consumption of less than one glass monthly, clear risks surfaced in three different areas: all-cause mortality, mortality from cardiovascular disease, and mortality from digestive diseases. (*See Table 1.*)

In this study, total soft drink consumption was not associated with overall risk of death from overall cancer, but there was an association with a higher risk of death from colorectal cancer (HR = 1.25). Total soft drink consumption was also associated with a higher risk of Parkinson's disease mortality (HR = 1.59). Controlling for body mass index did not change results significantly.

As with any observational study, these results must be viewed with caution regarding causality. One of the strengths of the study is the impressively large number of participants and follow-up years, as well as the multiple sites transcending geographical boundaries. Yet, this strength also results in heterogeneity of methods (i.e.,

Table 1. Mortality by Cause and Soft Drink Consumption			
	All-Cause Mortality	**Mortality Related to Cardiovascular Disease**	**Mortality Related to Digstive Diseases**
Total soft drinks	HR 1.17; 95% CI, 1.11-1.22 ($P < 0.001$)	HR 1.27 95% CI, 1.14 -1.40 ($P < 0.001$)	HR 1.50; 95% CI, 1.24-1.81 ($P < 0.001$)
Sugar-sweetened soft drinks	HR 1.08; 95% CI, 1.01-1.16 ($P = 0.004$)	HR 1.11, 95% CI, 0.95-1.30 ($P = 0.16$)	HR 1.59 95% CI, 1.24-2.05 ($P < 0.001$)
Artifically sweetened soft drinks	HR 1.26 95% CI, 1.16-1.35 ($P < 0.001$)	HR 1.52 95% CI, 1.30-1.78 ($P < 0.001$)	HR 0.99 95% CI, 0.65-1.50 ($P = 0.78$)
HR: hazard ratio; CI: confidence interval			

dietary recall), possibly leading to some built-in biases and confounding of results.

The clinician is on solid ground informing patients that there is mounting evidence that soft drink consumption of any type (artificially or sugar-sweetened) is linked to earlier death, and that this link is not necessarily related directly to obesity or diabetes. Although drinking an occasional soft drink does not appear to be linked to higher mortality risk, there are clear indications that more regular use is associated with health risks. This is an additional reminder of the importance and benefit of including a dietary assessment in health visits, especially when creating a comprehensive, patient-centered health and wellness plan. ■

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LONGEVITY

ABSTRACT & COMMENTARY

Optimism (Hopefully!) Increases Odds of 'Exceptional Longevity'

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

SYNOPSIS: Analysis of 10-year follow-up data from the Nurses' Health Study and 30-year follow-up data from the Veteran Affairs Normative Aging Study show a significant association between baseline levels of higher optimism and longevity, even when data is adjusted for health behaviors and psychosocial factors.

SOURCE: Lee LO, et al. Optimism is associated with exceptional longevity in 2 epidemiologic cohorts of men and women. *Proc Natl Acad Sci U S A* 2019;116:18357-18362.

In a landmark 1910 address to The College of Physicians and Surgeons, the reigning president, Dr. E.L. Trudeau, known for his innovative approach in treatment of tuberculosis, spoke about the importance of optimism in medicine.[1] He ended his speech with a quotation from one of his own patients, literary giant Robert Louis Stevenson: "To travel hopefully is a better thing than to arrive and the true success is in the labour."[2] Dr. Trudeau, experiencing illness from the perspective of both a physician and a tuberculosis patient himself, felt strongly that an optimistic physician conveys this stance to patients, and that this interaction enhances both healing and recovery for the patient.[1,3]

A review of publications since that time shows bursts of interest in this relationship, with more rigorous studies appearing in more recent years.[4] Lee et al noted that the current research supports an association of optimism with a reduced risk of cardiovascular disease, lung function deterioration, and premature mortality, but that there are no studies looking at optimism and life span. Specifically, Lee et al were interested in a relationship between optimism and "exceptional longevity," which they defined as survival to 85 years of age or older. To address this knowledge gap, the team looked at data from two long-term, broad-based, prospective investigations: the Nurses' Health Study (NHS) and the Veterans Affairs Normative Aging Study (NAS).

The NHS, currently in its third generation, launched in 1976 with periodic questionnaires designed to collect information about the potential for long-term side effects from the use of oral contraceptives. Very quickly, the researchers expanded the scope of the project to collect information on a variety of lifestyle factors, behaviors, and psychosocial factors influencing more than 30 chronic diseases. In 2004, an optimism assessment was included in the questionnaire. For the purposes of this study, mortality information was tracked until 2014.[5]

The NAS dates its birth to 1963. Devised as a longitudinal study on "non-pathological" aging, about 2,000 male veterans from diverse socioeconomic backgrounds agreed to periodic outpatient assessments during their lifetime. In 1989, the assessment included an optimism scale and mortality in these subjects has been tracked until 2016.[6]

The tools used to assess optimism for these two groups were different. The NHS used the Life Orientation Test-Revised (LOT-R) while the NAS employed a subsection of the Minnesota Multiphasic Personality Inventory-2. (MMPI 2). Previous research regarding these tools allowed correlation of optimism scores, with results from the NHS divided into quartiles and results from the more broadly based NAS placed into quintiles.

The LOT-R is a self-administered questionnaire asking for relative agreement or disagreement with 12 statements regarding general expectations. For example: "In uncertain times, I usually expect the best."[7]

The perhaps more widely known MMPI includes an optimism and pessimism scale. This test approaches measurement of optimism in a slightly different manner, looking at responses on the broader MMPI and analyzes the style of responses as more pessimistic or optimistic in general.[8]

Analysis included results for three different models based on 69,744 women respondents from NHS and 1,429 men from NAS. The first model is adjusted for social demographics such as race, age, education, and marital status; the second is adjusted for demographics and health conditions such as high cholesterol, depression, cancer, and stroke at baseline; the third is adjusted for demographics, health conditions, and health behaviors such as smoking, alcohol use, physical activity, and diet.

Summary Points

- Data from over 69,000 women participating in the Nurses Health Study (NHS) and from 1,429 men participating in the Veterans Affairs Normative Aging Study (NAS) was analyzed in search of an association between optimism and longevity.
- After adjustment for health conditions and demographics, women with optimism levels in the highest quartile had a 14.9% longer lifespan than women in the lowest quartile; for men, the equivalent comparison was a 10.9% longer lifespan (comparing highest to lowest levels of optimism).

Results for each model in each cohort showed association of higher levels of optimism with longer life span (P trend < 0.0001 for NHS and P trend = 0.002 for NAS). In both groups, results were attenuated for the third model (adding adjustment for health behaviors). In other words, when adjusting results but for health behaviors such as smoking, alcohol use, or diet in addition to demographics and health conditions, having a baseline high level of optimism was still significant, but less of a factor toward an increase in life span.

Lee et al also looked at the likelihood of survival to at least 85 years of age (exceptional longevity) by shrinking the pool of respondents to only those born early enough to reach this age by the end of the follow-up period. This approach allowed analysis of results from 13,045 women in the NHS and 1,117 men from the NAS. A similar pattern to the original analysis emerged, with higher optimism associated with greater odds of reaching exceptional longevity, and attenuation of these results with adjustment for health behaviors. The P trend was < 0.01 for both of the cohorts before adjustment for health behaviors.

■ COMMENTARY

Headlines reveal that the press was interested in this study. From "How to be more positive: Study links optimism to longevity" on Today.com[9] and "Want to live longer? Be an optimist" on CNN,[10] to a more skeptical *Forbes*: "Optimism, the key to longevity?"[11] It was clear that this research struck a chord.

While longevity is of general interest to the public, the implications of achieving exceptional longevity for public health policy and population health are of particular significance to the medical world. Yet, a close look at the study reveals some strengths but also some glaring gaps, making hard and fast conclusions difficult to support.

Perhaps the largest strength of the study resides in numbers: the exceptionally large number of respondents (1,429 in NAS and 69,744 in NHS) and the 10-30 years of follow-up. While this robust data lends credibility to the results, replication of the study faces significant hurdles. Additionally, the participants by definition are drawn from relatively homogenous pools (especially in the NHS cohort) and the overwhelming majority of the participants are women, limiting the ability to generalize the findings.

Another concerning factor is that in both the NHS and the NAS cohorts, optimism was measured only once — at baseline. There is no way to know if these measures were stable over time. The results from both studies attenuated when health behaviors, such as smoking and alcohol use, were considered. This certainly may be due to a link between optimism and healthy behaviors, but clear evidence that optimism scores remained stable would be helpful to advance knowledge regarding these relationships.

All patients enrolled in the NHS and NAS were adults by the time of the initial optimism assessment. Future studies are needed to understand how optimism develops over time, the relative stability of this trait, and any relationship to health benefits and longevity. For the present time, we know only that a higher level of optimism during middle-age years was associated with greater longevity and greater odds of reaching exceptional longevity in two long-term, prospective studies.

Notably, this study tells us nothing about if we can affect or change optimism in adults or help develop optimism in children. Furthermore, it does not tell us if changing optimism at any stage of life is associated with health benefits.

As noted earlier, the concept of optimism as a healing force in medicine is not new. When Dr. E.L. Trudeau spoke about optimism in medicine in the early 1900s, he was explicitly referring to the optimism of physicians. He felt an optimistic physician conveyed this attitude to patients, and thus, promoted healing.[1,2] More than 100 years later, this work by Lee et al demonstrates how far we have come in our understanding of optimism in medicine and suggests a path to further our understanding.

For now, we can tell patients that attitude and a positive outlook may help with lengthening life span and achieving exceptional longevity. Working toward a more optimistic approach to life may not come easily to many of our patients and may not feel natural for a provider. In speaking with patients, listen for echoes of self-blame For example, "I have caused my own health problems because of my pessimism." When a provider acknowledges the difficulties inherent in such a change it can be reassuring and affirming for patients. Remind patients that optimism occurs on a gradient and that looking for incremental movement may be achievable and more palatable for many.

In addition, this study also may serve as a reminder of the added value of understanding and addressing psychological factors while interviewing patients, and

Table 1. Significant Results Between the Nurses' Health Study and the Veterans Affairs Normative Aging Study

	Percent Difference in Life Span NHS (n = 69,744) Quartile 4 vs. Quartile 1	Percent Difference in Life Span NAS (n = 1,429) Quintile 5 vs. Quintile 1	Odds Ratio for Survival to Age 85+ years NHS (n = 13,045) Quartile 4 vs. Quartile 1	Odds Ratio for Survival to Age 85+ Years NAS (n = 1117) Quintile 5 vs. Quintile 1
Model 1: Adjusted for demographics	18.6% (95% CI, 15.4-21.8)	14.0% (95% CI, 4.5-24.4)	1.6 (95% CI, 1.3-1.9)	1.8 (95% CI, 1.2-2.7)
Model 2: Adjusted for demographics and health conditions	14.9% (95% CI, 11.9-18.0)	10.9% (95% CI, 1.3-21.5)	1.5 (95% CI, 1.2-1.7)	1.7 (95% CI, 1.1-2.5)
Model 3: Adjusted for demographics, health conditions, and health behaviors	8.7% (95% CI, 5.8-11.6)	9.8% (95% CI, 0.3-20.3)	1.2 (95% CI, 1.0-1.5)	1.6 (95% CI, 1.0-2.4)

NHS: Nurses' Health Study; NAS: Normative Aging Study
Comparison of high vs. low levels of optimism in the two study cohorts (NHS and NAS) for difference in life span and odds of achieving age 85 years or older. Optimism was rated in four levels (quartiles) in the NHS study and five levels (quintiles) in the NAS study. Quartile 4 and quintile 5 represented the highest level of optimism in the NHS and NAS, respectively.

the intrinsic value of appreciating such traits when developing comprehensive wellness and treatment plans. ■

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CME QUESTIONS

1. Which of the following is a common transient side effect of oral peppermint oil?
a. Constipation
b. Diarrhea
c. Dry mouth
d. Heartburn

2. A vegetarian diet as compared to a diet inclusive of red meat increases risk for which of the following?
a. Ischemic stroke
b. Acute myocardial infarction
c. Ischemic heart disease
d. Hemorrhagic stroke

3. Which of the following is true about the benefits of lavender oil aromatherapy in people being treated for cancer with chemotherapy?
a. It led to marked improvements in State, or short-term, anxiety over the treatment period.
b. It led to benefits in sleep, but tea tree oil did not.
c. It led to benefits in Trait, or chronic, anxiety over the treatment period, but tea tree oil and the control group did not show such benefits.
d. It led to no benefits in any of the variables measured when compared to the placebo group.

4. What did Lee et al find regarding optimism and life span?
a. Even though levels of optimism may change over time, this study provides the field with suggestive evidence of a link between higher level of optimism in men and women and longevity.
b. A level of optimism is difficult to access, may change over time, and cannot be accurately measured, thus a more accurate measure must be developed before further studies looking into any associated health benefits are conducted.
c. Optimism in medicine is an old, outdated concept, developed in response to lack of broad-based medical information and investigative techniques.
d. Even though levels of optimism may change over time, the study by Lee et al provides the field with suggestive evidence of a link between higher level of optimism in women and longevity; the findings among men are less impressive and need further investigation before making even preliminary conclusions.

[IN FUTURE ISSUES]

Association Between Gluten Intake and Celiac Disease

The Health Effects of Magnesium: Part 2

Nut Consumption and Weight Change