

Integrative Medicine

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

CARDIOVASCULAR DISEASE

ABSTRACT & COMMENTARY

Aerobic Exercise and Heart Health: Is It Ever Too Late to Start?

By *Eric Neilson, MD, and Nancy Selfridge, MD*

Dr. Neilson is Assistant Professor, Department of Clinical Medicine, Ross University School of Medicine, Commonwealth of Dominica, West Indies. Dr. Selfridge is Professor and Chair, Department of Clinical Medicine, Ross University School of Medicine, Commonwealth of Dominica, West Indies.

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

SYNOPSIS: In this prospective, randomized, controlled trial, researchers demonstrated improvements in exercise tolerance and diastolic cardiac function in middle-aged, healthy, sedentary men and women performing intensive aerobic exercise over a two-year period.

SOURCE: Howden EJ, Sarma S, Lawley JS, et al. Reversing the cardiac effects of sedentary aging in middle age — a randomized controlled trial: Implications for heart failure prevention. *Circulation* 2018;137:1549-1560.

Hear failure (HF) is a common, debilitating, and often fatal disease. Heart failure with preserved ejection fraction (HFpEF) makes up about half of heart failure diagnoses and is associated with increasing ventricular stiffness (loss of compliance) and consequent diastolic dysfunction. Further, there is no highly effective pharmacologic treatment for HFpEF.¹ Two leading risk factors for the development of HFpEF are aging and sedentary lifestyle, and fitness in middle age is a strong predictor of future heart

failure.² Competitive master athletes (defined as 35 to 100 years of age) maintain ventricular compliance similar to younger individuals. Howden et al previously found that exercise initiated after age 65 years or in patients with already established HFpEF, although associated with increased quality of life and fitness measures, cannot significantly improve ventricular stiffness resulting from sedentary aging.^{3,4} Thus, they conducted this study to determine if there was a point in the aging process in which exercise could reverse

Financial Disclosure: *Integrative Medicine Alert's* Executive Editor David Kiefer, MD; Peer Reviewer Suhani Bora, MD; Relias Media Executive Editor Leslie Coplin; Editor Jonathan Springston; and Editorial Group Manager Terrey L. Hatcher report no financial relationships relevant to this field of study.

[INSIDE]

Does Improving Sleep
Improve
Mental Health?
page 100

B Vitamins
and Hip Fracture Risk
page 103

Tele-yoga
for Chronic Pain
page 105

Vitamin C and
Postoperative Atrial
Fibrillation Risk
page 107

Integrative Medicine Alert (ISSN 1096-942X) is published 12 times annually by Relias LLC, 111 Corning Road, Suite 250, Cary, NC 27518-9238.

Periodicals Postage Paid at Cary, NC, and additional mailing offices.

GST Registration Number: R128870672.

POSTMASTER: Send address changes to Integrative Medicine Alert, Relias LLC, 111 Corning Road, Suite 250, Cary, NC 27518-9238.

© 2018 Relias LLC. All rights reserved. No part of this newsletter may be reproduced in any form or incorporated into any information-retrieval system without the written permission of the copyright owner.

This is an educational publication designed to present scientific information and opinion to health professionals, to stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. Opinions expressed are not necessarily those of this publication. Mention of products or services does not constitute endorsement. Professional counsel should be sought for specific situations. This publication is not intended for use by the layman.

SUBSCRIBER INFORMATION

(800) 688-2421
customerservice@reliamedia.com
ReliasMedia.com

Questions & Comments:

Please contact Executive Editor Leslie Coplin, at lcoplin@relias.com

Subscription Prices

United States
Print: 1 year with free AMA PRA Category 1 Credits™, \$319
Add \$19.99 for shipping & handling.
Online only: 1 year (Single user) with free AMA PRA Category 1 Credits™, \$269

Multiple Copies: Discounts are available for group subscriptions, multiple copies, site-licenses, or electronic distribution.
For pricing information, please contact our Group Account Managers at groups@reliamedia.com or (866) 213-0844.

Back issues: \$42. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

Canada: Add 7% GST and \$30 shipping.
Elsewhere: Add \$30 shipping.

ACCREDITATION

Relias LLC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Relias LLC designates this enduring material for a maximum of 3 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

The American Osteopathic Association has approved this continuing education activity for up to 2 AOA Category 2-B credits.

This CME activity is intended for physicians and researchers interested in integrative medicine. It is in effect for 36 months from the date of the publication.

Summary Points

- An intensive personalized and graded exercise training program for middle-aged (53 ± 5 years), sedentary (no prior history of consistent exercise > 30 minutes three times weekly) but otherwise healthy men and women showed improvements in oxygen consumption, cardiac stiffness, and left ventricular diastolic pressure-volume relationships.
- Improvements correlated with stepwise monitored progression to five to six hours of aerobic exercise each week, including two weekly high-intensity interval training sessions, over a 10-month period. Improvements were maintained over an additional 14 months with 150 to 180 minutes of exercise/week, including one high-intensity interval training session.
- Implications for non-whites and those with pre-existing heart disease or risk factors for heart disease, including obesity, are unknown; the study was insufficiently powered to draw valid conclusions for women as a sub-group.

ventricular stiffness with associated implications for reducing the risk of future heart failure.

Capitalizing on accumulated evidence that high-intensity interval training (HIIT) provides significant improvements in cardiovascular fitness over moderate-intensity exercise^{5,6} and that an inverse dose-response relationship exists between physical activity and risk of heart failure,⁷ Howden et al demonstrated that performing a highly structured endurance exercise regimen over two years improved cardiac stiffness and cardiorespiratory fitness in sedentary but otherwise healthy, middle-aged individuals (53 ± 5 years).

The study included 53 participants, about half female ($n = 33$), with a sedentary lifestyle (no prior history of consistent exercise > 30 minutes three times weekly) and no history or evidence of comorbidities including tobacco use, hypertension, obesity, untreated thyroid disease, chronic lung disease, obstructive sleep apnea, or coronary artery disease. Participants were randomized into either an aerobic and resistance endurance training program (ExT) or a flexibility and balance training/yoga control group. All participants had pretest baseline measures of fitness, exercise capacity, and cardiac function, including echocardiography and cardiac catheterization with manipulations of

cardiac filling (preload) using lower-body negative pressure techniques and isotonic saline IV fluid loads, to determine myocardial stiffness measures.

Endurance exercise training included an individualized progressive approach based on baseline measures of fitness, beginning with two to three 30-minute sessions per week and progressing over 10 months to five to six hours per week, including two days of HIIT sessions (four four-minute, 95% maximum exercise intervals separated by three-minute active recovery intervals), a recovery day of light aerobic activity after each HIIT day, one long (at least 60 minutes) and one 30-minute sub-maximum effort session. For the final 14 months, HIIT was reduced to one session per week. The control group participated in yoga, balance, and strength training activities three times per week for two years without incorporation of any aerobic exercise and with a caveat to avoid hot yoga classes or prolonged endurance activities.

All participants in both groups met monthly with a physiologist, and exercise was monitored and compliance documented using exercise logs and a heart rate monitor. Overall mean adherence rate to the ExT intervention was a surprising 88% ($\pm 11\%$). The adherence rate in the control group was not detailed in the report, although

five individuals out of 32 withdrew during the study (citing work commitments, prior injury, personal reasons, and health reasons). Fifty-two participants completed the two-year study; one participant withdrew after the pretest studies were completed.

The ExT intervention at 10 months resulted in an 18% increase in mean $\text{VO}_{2\text{max}}$ (95% confidence interval [CI], 15-22%; $P < 0.05$), with a slight decrease noted in the control group of -1% (95% CI, 4.8-2.7%; $P < 0.05$). No additional changes were noted in the ensuing 14 months for either group. Left ventricular end-diastolic volume measured by echocardiography (correlating with ventricular compliance) showed a similar pattern of increasing by about 17% in the ExT group and no change in the control group, with maximum effect at 10 months. After two years, pretest procedures were repeated in all participants to assess left ventricular end-diastolic pressure volume and cardiac stiffness models. Participants in the ExT group demonstrated statistically significant ($P < 0.05$) decreases in mean resting heart rate from 63 bpm (95% CI, 60-67) pre-intervention to 58 bpm (95% CI, 55-61) post-intervention, with no change pre- and post- noted in the controls. Increases in mean stroke volume index for the ExT group also were significant from 42 mL/m² (95% CI, 39-45) to 45 mL/m² (95% CI, 42-49) compared to no change in the control group 41 mL/m² (95% CI, 38-43) to 42 mL/m² (95% CI, 39-44). Statistically significant changes ($P < 0.05$) also were noted in end-diastolic volume index and transmural pressures correlating with increased left ventricular compliance and indicating an overall improvement in diastolic function. No statistically significant changes in any of these parameters were noted in the control group, indicating that the control intervention exercise program did not confer the benefits of increased left ventricular compliance that were evident from the HIIT/aerobic/endurance program.

■ COMMENTARY

This study is the next step in establishing prescriptive lifestyle changes aimed at preventing or postponing the development of HF. From 2001 to 2014, 6.5 million Americans were diagnosed with HF. With an aging population over the next 10 years, this number is expected to increase to more than 8 million. Overall, one-year mortality in Medicare patients with HF is nearly 30%. Data showed HF was a principal diagnosis in approximately 900,000 hospital discharges, more than 2.3 million physician office visits, and more than 450,000 emergency department visits. In 2012, cost estimates due to HF were more than

\$30 billion and are expected to rise to nearly \$70 billion by 2030.⁸

We know lifestyle choices, including exercise, are key determinants of cardiovascular health. The American Heart Association (AHA) 2018 update on Heart Disease and Stroke⁸ indicates the number of adults exercising enough is a mere 21.5%, leading to one of the seven AHA goals for heart health: at least 150 minutes of weekly exercise, including incorporating vigorous exercise activities. Participants in the ExT arm of this study adhered to these recommendations, averaging 150-180 minutes/week with incorporation of HIIT. However, they did so in a highly individualized, structured, progressive, and supervised program, elements that clearly could overcome common barriers to adherence to exercise recommendations for sedentary individuals. Such a program would prove prohibitive to many if it was associated with any cost not covered by insurance.

Additionally, there are important questions to be answered about the general applicability of this study as a preventive recommendation. Although these participants were sedentary, none had comorbidities or major risk factors associated with cardiac disease. The average body mass index of participants was 26 kg/m², the lower range of “overweight” and not representative of a large subset of sedentary and at-risk Americans. None had used tobacco in the last 10 years. The study was limited to 33 women, one black, and two Hispanic participants. African Americans have the highest risk of HF. Of the nearly 1 million people newly diagnosed with HF each year, half are women.¹ This study was insufficiently powered to allow for statistically significant interpretation of results for these important demographic groups. Further studies focused on these groups will be necessary to determine if this exercise intervention is a viable strategy for preventing the devastating effect of HF.

Currently, the exercise volume maintained in the ExT group in this study aligns with current AHA recommendations of about 150 minutes/per week. The study included one HIIT session per week, and although no adverse events due to the ExT program were reported, the participants were carefully selected and closely monitored, unlike most individuals who initiate exercise programs. The volume and intensity of this exercise program could not and should not be initiated by sedentary middle-aged adults without supervision and baseline assessment of cardiac health. Although this study adds much in terms of understanding

the physiology of the aging heart and the capacity to reverse age-related changes, we already have substantial evidence that AHA exercise recommendations are associated with reduced overall morbidity and mortality. These recommendations should not change. Additional studies are needed in a wider range of more representative U.S. populations to determine if the authors' exercise intervention can improve diastolic function due to aging in these groups. ■

REFERENCES

1. Mijjkovic LV, Spiroska V. Heart failure with preserved ejection fraction—concept, pathophysiology, diagnosis and challenges for treatment. *Open Access Maced J Med Sci* 2015;3:521-527.
2. Arbab-Zadeh A, Dijk E, Prasad A, et al. Effect of aging and physical activity on left ventricular compliance. *Circulation* 2004;110:1799-1805.
3. Fujimoto N, Hastings JL, Carrick-Ranson G, et al. Cardiovascular effects of 1 year of alagebrium and endurance exercise training in healthy older individuals. *Circ Heart Fail* 2013;6:1155-1164.
4. Fujimoto N, Prasad A, Hastings JL, et al. Cardiovascular effects of 1 year of progressive endurance exercise training in patients with heart failure with preserved ejection fraction. *Am Heart J* 2012;164:869-877.
5. Weston KS, Wisloff U, Coombes JS. High-intensity interval training in patients with lifestyle-induced cardiometabolic disease: A systematic review and meta-analysis. *Br J Sports Med* 2014;48:1227-1234.
6. Hannan AL, Hing W, Simas V, et al. High-intensity interval training versus moderate-intensity continuous training within cardiac rehabilitation: A systematic review and meta-analysis. *Open Access J Sports Med* 2018;9:1-17.
7. Pandey A, Garg S, Khunger M, et al. Dose-response relationship between physical activity and risk of heart failure: A meta-analysis. *Circulation* 2015;132:1786-1794.
8. AHA Statistical Update: Heart Disease and Stroke-2018 Update. *Circulation* 2018;137:e67-e492.

INSOMNIA

ABSTRACT & COMMENTARY

Chicken or Egg: Does Improving Sleep Improve Mental Health?

By Ellen Feldman, MD

Altru Health System, Grand Forks, ND

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

SYNOPSIS: Authors of this large, randomized, controlled study strongly suggest that better sleep leads to improvement in several areas of mental health, and that a digital form of cognitive behavior therapy can significantly help in treatment of insomnia.

SOURCE: Freeman D, Sheaves B, Goodwin GM, et al. The effects of improving sleep on mental health (OASIS): A randomised controlled trial with mediation analysis. *Lancet Psychiatry* 2017;4:749-758.

Sleep is a basic need. Leaping over geographical and cultural barriers, disorders of sleep affect patients of all ages and genders worldwide.¹ A common disorder of sleep, insomnia is defined broadly as difficulty initiating or staying asleep. Given that individuals' sleep requirements vary, insomnia becomes clinically significant when a patient perceives impairment or functional interference from the sleep disturbance.²

About 10% of patients in primary care clinics have insomnia, but this commonly is overlooked as a diagnosis or factor behind other seemingly unrelated complaints. Insomnia lasting more than one month (chronic insomnia) negatively affects daytime alertness, attention, and cognitive processing. Even shorter bouts of insomnia may affect frequency of headaches, levels of energy, pain, and other medical conditions.^{1,2,3}

Although we know many mental health diagnoses affect sleep, there is growing evidence that

sleep disruption itself can lead to mood disorders and thought disorders. With an interest in better understanding the relationship between sleep and mental health, Freeman et al designed a study to investigate the effects of sleep improvement alone on psychotic symptoms (such as paranoia and hallucinations), depression, and anxiety.

The study was designed as a single-blind, randomized, controlled trial of digital cognitive behavioral therapy (CBT) vs. treatment as usual. To promote diversity, participants were recruited from 26 universities across the United Kingdom. All recruitment was via email or website advertisement. Eligibility was quite broad: Participants needed to be enrolled at the university and score 16 or lower on the sleep condition indicator (SCI), an eight-item screening tool for insomnia.⁴

Notably, a score of ≤ 16 on the SCI generally is accepted as a cutoff for insomnia disorder. The questions on the SCI look at several aspects of sleep,

Summary Points

- The authors randomized 3,755 university students with positive screens for insomnia to receive either online cognitive behavioral therapy (CBT) via a sleep-oriented program, aptly named Sleepio, or treatment as usual.
- The primary outcome measures were insomnia, paranoia, and hallucinations; secondary measures included depression and anxiety.
- At week 10, the group receiving digital CBT had significantly reduced insomnia compared to the usual treatment group ($P < 0.0001$); all other outcome measures decreased significantly.
- Statistical analysis suggests that lengthening hours of sleep mediates improvement in psychotic symptoms, depression, and anxiety.

including quantity and quality of sleep, as well as effect on daytime functioning. Higher scores on the SCI (up to 32) indicate better sleep in general.⁴

The authors randomly assigned 3,755 participants to treatment, with 1,891 subjects in the CBT group and 1,864 in the treatment as usual group. Assessment of multiple outcomes, including insomnia (defined as difficulty initiating or staying asleep and leading to functional impairment), paranoia, hallucinations, symptoms of depression, mania, and psychological well-being, were conducted via online scales at baseline and specified intervals.

The digital form of CBT used to treat insomnia in this study is called Sleepio. This online program and app can be completed in six sessions on any browser and each session lasts about 20 minutes. An initial online assessment determines a personalized, interactive program that includes educational, behavioral, and cognitive sections. Among the techniques used are relaxation, sleep restriction (restricting sleep to certain times), imagery, and sleep hygiene. Sleep diaries play a central role in this approach and allow an animated sleep therapist to propose new sleep windows and interventions based on the sleep diary data.⁵

Participants were asked to complete online screens measuring the outcomes at baseline, week 3, week 10, and week 22. The week 3 measurement was

inserted to help understand timing of the improvements (that is, to try to determine if sleep improved before or after changes in mental health symptoms). At each assessment, subjects were asked about any contact with mental health services, any medication changes, or any new psychological therapy.

Completion of assessments and treatment were low. In both groups, more than 50% of the participants did not complete the assessments, and only 18% of the initial 1,891 subjects in the CBT arm completed the entire six-session course of Sleepio.

However, even controlling for the dropout rate, when compared with the control group, there was significant improvement in SCI scores, indicating improvement in sleep quantity and quality, paranoia, and hallucinations at every measurement point (all P values < 0.001). Table 1 shows data for insomnia from weeks 10 and 22.

Freeman et al sought to determine if the sleep improvement mediated the changes in paranoia and hallucinations. Mediation analysis determined that improvement in sleep by week 3 could be responsible for about half of the total reduction in psychotic experiences reported by week 22.

Scales measuring depressive symptoms, anxiety, and psychological well-being all showed sustained improvement over the course of the study. (See Tables 2-4.) Other notable findings were that the two study arms were matched evenly for contact with mental health services during the trial period. No adverse events were reported. However, the mean score on the mania scale was increased slightly in the intervention group.

■ COMMENTARY

On the surface, this investigation of the relationship between sleep improvement and mental health disorders may be viewed as a study of primary interest to providers treating patients with mental health impairments. However, on second glance, the applicability of this study to a wider range of patients is clear.

The main goal of this study — determining if sleep improvement decreases mental health impairment — required first achieving significant sleep improvement. A large number of participants was needed to power the study. The 3,755 subjects were all university students with insomnia, only some of whom had mental health problems. For ease of application and accessibility to university students across the United Kingdom, digital CBT

Table 1: Mean Score SCI, Weeks 10 and 22

	Mean score for insomnia measured with SCI-8 on 32-point scale, week 10	Mean score for insomnia measured with SCI-8 on 32-point scale, week 22
Intervention group (digital cognitive behavioral therapy, "Sleepio")	18.08 (SD = 6.66)	19.27 (SD = 7.13)
Control group (treatment as usual)	13.31 (SD = 6.45)	14.43 (SD = 6.71)
<i>P</i> value	< 0.001	< 0.001

Sleep condition indicator (SCI) cutoff score for insomnia disorder is ≤ 16.

was chosen as the intervention to improve sleep. The results in sleep improvement alone are impressive and seem to have widespread relevance to this population.

Freeman et al noted that these results very well may be applicable to a larger adult population, as Sleepio was developed for adults and there was no modification in protocol for this student population. In fact, the significant improvement in sleep in this study is similar to the improvement in sleep found in previously published trials with general adult participants.

Although part of the excitement from the study results is linked to the reduction of insomnia with internet-based CBT, that was not the primary aim of this study. The primary focus was to determine if the reduction in insomnia would reduce emergence of paranoia and hallucinations. The secondary focus was determine if the intervention improved depression and anxiety symptoms while helping psychological well-being. The significant results and mediation analysis point to a direct (but not complete) link between improvement in sleep and these other outcome measures.

Some clear limitations of this study include the high dropout rate, the reliance on self-reported questionnaires, the self-selection of participants, and the lack of exclusion criteria. All of these factors may have introduced bias into the results. In particular, the high rate of noncompletion of the entire Sleepio protocol most likely skewed the results, as it is unknown why the participants stopped the treatment. The dropout rate in this study is similar to other online digital CBT trials;⁶ future direction in this field should include an investigation into characteristics of participants who are most likely to complete the protocol. Continuing efforts to involve broad representative populations as participants will be useful as well.

It is unclear from this study if there is a clinical significance to the slight increase in mean scores

Table 2: Depression Measured via Patient Health Questionnaire (PHQ-9)

	Control group (treatment as usual)	Intervention group (digital CBT-Sleepio)
Week 10	11.27	8.44
Week 22	10.34	8.00

CBT: cognitive behavioral therapy; mean values; *P* < 0.0001

Table 3: Anxiety Measured via Generalized Anxiety Disorder 7 (GAD-7)

	Control group (treatment as usual)	Intervention group (digital CBT-Sleepio)
Week 10	8.35	6.53
Week 22	7.67	6.14

CBT: cognitive behavioral therapy; mean values; *P* < 0.0001

Table 4: Psychological Well-being Measured via Warwick-Edinburgh Mental Wellbeing Scale

	Control group (treatment as usual)	Intervention group (digital CBT-Sleepio)
Week 10	38.73	40.92
Week 22	39.63	42.12

CBT: cognitive behavioral therapy; mean values; *P* < 0.0001

on the mania scales in the group receiving digital CBT. It may be that this group actually was reporting elevated mood and energy, but this warrants further investigation before making firm conclusions.

Overall, the study results make it clear that when university students present with insomnia, addressing the sleep problem vigorously with digital CBT may reduce the severity of mental health symptoms, such as depression, anxiety, and even paranoia. A bit less clear, but strongly suggested, is that when university students present with mental health symptoms, addressing sleep issues

vigorously may lessen the severity of these symptoms.

As this was not a head-to-head comparison of interventions to improve sleep, we have no information regarding the efficacy of digital CBT compared to pharmacotherapy or other forms of psychotherapy. Obtaining good sleep or improving insomnia by any appropriate intervention may have the same effect. However, this conclusion is premature and requires future confirmation.

A take-home message for integrative and primary care providers: Strongly consider insomnia treatment as a focus for intervention when patients present with symptoms of mental health disorders. A review of the effect of CBT and awareness of the types of digital CBT may be useful in discussions with patients. Although we cannot conclude directly from this study which patients will benefit most from digital CBT, thinking about offering this technique for intervention opens new options in creating a comprehensive, individualized treatment

plan. The results of this study hold implications for future research on the pivotal role of sleep in mental health and validate the importance of addressing sleep quality and quantity in treatment of specific symptoms and disorders. ■

REFERENCES

1. Stranges S, Tigbe W, Gomez-Olive FX, et al. Sleep problems: An emerging global epidemic? Findings from the INDEPTH WHO-SAGE study among more than 40,000 older adults from 8 countries across Africa and Asia. *Sleep* 2012;35:1173-1181.
2. Grandner MA, Chakravorty S. Insomnia in primary care: Misreported, mishandled, and just plain missed. *J Clin Sleep Med* 2017;13:937-939.
3. Goodie JL, Hunter CL. Practical guidance for targeting insomnia in primary care settings. Available at: https://www.sbm.org/UserFiles/file/PracticalGuidanceforTargetingInsomniainPrimaryCareSettings_Goodie-Hunter_2014.pdf. Accessed July 16, 2018.
4. Espie CA, Kyle SD, Hames P, et al. The Sleep Condition Indicator: A clinical screening tool to evaluate insomnia disorder. *BMJ Open* 2014;4:e004183.
5. Sleepio. Available at: <https://www.sleepio.com/>. Accessed July 8, 2018.
6. Christensen H, Batterham PJ, Gosling JA, et al. Effectiveness of an online insomnia program (SHUTi) for prevention of depressive episodes (the GoodNight Study): A randomized controlled trial. *Lancet Psychiatry* 2016;3:333-341.

BONE HEALTH

ABSTRACT & COMMENTARY

B Vitamins and Hip Fracture Risk: To B or Not to B?

By Narelle Magloire, MD, and Nancy J. Selfridge, MD

Dr. Magloire is a Clinical Teaching Fellow in the Clinical Foundations Department at Ross University School of Medicine, Commonwealth of Dominica, West Indies. Dr. Selfridge is Professor and Chair, Clinical Foundations Department, Ross University School of Medicine, Commonwealth of Dominica, West Indies.

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

SYNOPSIS: Researchers conducted a secondary analysis and extended follow-up of two large, randomized, controlled trials to show the relationship between supplementing with B vitamins and the incidence of hip fractures.

SOURCE: Garcia Lopez M, Bønaa KH, Ebbing M, et al. B vitamins and hip fracture: Secondary analyses and extended follow-up of two large randomized controlled trials. *J Bone Miner Res* 2017;32:1981-1989.

Hip fractures are associated with significant healthcare costs, as well as morbidity, suffering, and mortality for patients. In an elderly frail patient, a hip fracture may precipitate a cascade of circumstances, including immobilization and hospitalization, that introduce potential for life-threatening events at worst and loss of independence and autonomy at best. Studies have demonstrated an association between elevated blood homocysteine levels and incidence of hip fracture and osteoporosis. Thus, it has been hypothesized that homocysteine-lowering agents might be beneficial in reducing hip fracture incidence.¹

B vitamins, particularly B12, B6 and folate, reduce homocysteine levels through their coenzyme functions in the methionine cycle, converting homocysteine to methionine, which then becomes incorporated into DNA and RNA, leading to building of proteins and lipids. Interventional trials using a randomized, controlled design to study the relationship between B vitamins and hip fractures are difficult to implement because such an infrequent primary outcome requires a large number of study participants to attain statistical significance. Accordingly, interventional studies to date have been limited in number, hampered by confounding

Summary Points

- Based on the observation that elevated homocysteine levels are associated with an increased risk of hip fractures, researchers investigated whether B vitamins, which are known homocysteine-lowering agents, might be associated with reduced risk of hip fracture.
- Vitamin B6 supplementation above the level of daily recommended doses is associated with an increased risk for hip fractures.
- The combination of folic acid and vitamin B12 supplementation did not show an overall reduction in hip fracture risk in the study participants, either during the study or in the extended follow-up.
- A secondary analysis demonstrated a decreased hip fracture incidence noted in women taking B12 with folate, compared to placebo; women represented only 23% of study participants.

variables (such as dietary composition), and have been unable to show a benefit solely attributable to B supplementation; however, observational studies have shown a small inverse association between vitamin B intake and hip fractures.^{1,2,3,4} To achieve the necessary sample size, Garcia Lopez et al performed a secondary analysis and extended follow-up of two large, randomized clinical trials previously conducted to study B vitamins as an intervention to reduce cardiovascular disease, determining if there was any effect between use of B vitamins and the risk of hip fracture.

The investigators analyzed pooled data from the Norwegian Vitamin Trial (NORVIT, December 1998 to March 2004) and the Western Norway B Vitamin Intervention Trial (WENBIT, January 2000 to October 2005), two randomized, placebo-controlled, double-blind clinical trials that included 6,837 participants. These trials were identical in design and originally looked at folic acid, vitamin B12, and vitamin B6 supplementation to reduce cardiovascular morbidity and mortality in patients with ischemic heart disease. Using a 2 × 2 factorial design, participants in these two studies were placed randomly in one of four groups to receive: 1) folic acid 0.8 mg, vitamin B12 0.4 mg, and vitamin B6 40 mg; 2) folic acid 0.8 mg and vitamin B12 0.4 mg; 3) vitamin B6 40 mg; and 4) placebo. In each group, men represented about 77% of study participants and women represented

Table 1: B Vitamin Intervention Doses Compared to Recommended Dietary Allowances (RDA)

Vitamin	Daily Study Dose	RDA
Folate	0.8 mg	0.4 mg/d
B12	0.4 mg	0.0024 mg/d
B6	40 mg	1.3 mg/d

about 23%. Table 1 shows study doses compared to recommended daily allowances for these vitamins.

Collection and analysis of blood samples for B vitamin and homocysteine levels occurred at baseline, at one to two months, and at the end of the intervention. Covariates considered in the analyses included age, sex, body mass index, smoking status, hypertension, diabetes, and the presence of the 5,10-methylenetetrahydrofolate reductase gene polymorphism associated with increased homocysteine levels.

The authors linked the combined dataset from NORVIT and WENBIT to the Norwegian hip fracture database. They used diagnostic and surgical procedure codes to identify incident hip fractures, and in cases that were not clear, they employed a comprehensive decision-making algorithm. The primary outcome was defined as a new or first hip fracture sustained by a trial participant within the study period, extended to include a post-trial follow-up observation period through December 2012. Mean plasma homocysteine levels were similar in all groups at baseline prior to intervention and were not significantly elevated, around $12 \pm 5 \mu\text{mol/L}$.

No statistically significant difference in hip fracture incidence was noted in the vitamin B12 + folate group compared to placebo. The two groups receiving any B6 supplementation demonstrated a statistically significant increase in hip fractures at 42% compared to placebo during the post-trial follow-up ($P = 0.008$; 95% confidence interval [CI], 9-83%), a difference not apparent during the trial period analysis. Individuals experiencing fractures had mean plasma homocysteine levels of $13.6 \pm 5.2 \mu\text{mol/L}$ compared to $12.2 \pm 5.0 \mu\text{mol/L}$ in those with no fractures ($P < 0.01$). Overall, fracture events were rare. Total fractures numbered only 43 during the trial and 236 during the post-trial follow-up out of the total 6,837 participants. When a secondary analysis was performed, a statistically significant decrease in fracture

incidence was noted in women receiving B12 and folate compared to placebo (hazard ratio, 1.87; 95% CI, 1.14-3.07), a relationship not noted in men within this group.

■ COMMENTARY

The prevention of hip fractures is a high priority because of the effect on patients, families, communities, and economies.⁵ Although homocysteine appears to be a marker for increased risk of hip fracture, homocysteine-lowering therapy, in particular B vitamin supplementation, has not demonstrated success in reducing fracture risk in clinical trials.^{2,3,4} This analysis of two large Norwegian trials examining B vitamin supplementation, although adequately powered, also failed to show a preventive benefit for the population studied.

In addition to the size of the study population and the addition of the extended follow-up, study strengths include the blood analysis results that analyzed baseline mean homocysteine levels and the effects of supplementation, showing that B12 and folate supplementation (with or without B6) had a statistically significant effect on lowering homocysteine levels, whereas placebo and B6 did not. In fact, any B6 supplementation appeared to increase fracture risk, an effect not mitigated by the addition of B12 and folate. Secondary stratified analyses for multiple factors known to affect risk of osteoporosis and hip fractures were another strength. Only female gender emerged as a covariate having an effect on outcomes, and this was only for women taking folate and B12.

A study weakness is that data were pooled from participants who all had underlying ischemic heart disease in the original studies, and who were relatively young (51-73 years of age) considering the primary outcome of hip fracture. Further, only 23% of participants were women; thus, the

majority of study participants were not representative of the aging population at greatest risk. The results may not be generalizable to a more diverse or representative population. Dietary data were not collected in this study. Although plasma B vitamin levels were monitored at baseline and during intervention, other dietary factors, such as calcium, magnesium, vitamin D, and protein intake, influence fracture risk.

When patients seek advice about vitamin supplementation, providers can share that supplementation with B12 and folate appears to lower homocysteine levels, but no benefit is apparent in reducing hip fracture risk except in women. Supplementation with B6 at levels significantly greater than the recommended daily allowance should be discouraged because of the clear association with increased hip fracture risk. In the meantime, we await additional bench research to clarify complex biochemical and physiologic relationships, including the role of homocysteine, in the development of osteoporosis and related fracture risk. ■

REFERENCES

1. Gjesdal CG, Vollset SE, Ueland PM, et al. Plasma homocysteine, folate and vitamin B12 and the risk of hip fracture; the Hordaland homocysteine study. *J Bone Miner Res* 2007;22:747-756.
2. Koh ZD, Wang R, Ang LW, et al. Dietary B vitamin intake and risk of hip fracture: The Singapore Chinese Health study. *Osteoporos Int* 2013;7:2049-2059.
3. Van Wijngaarden JP, Swart KM, Enneman AWW, et al. Effect of daily vitamin B-12 and folic acid supplementation on fracture incidence in elderly individuals with an elevated plasma homocysteine concentration: B-PROOF, a randomized controlled trial. *Am J Clin Nutr* 2014;100:1578-1586.
4. Gommens J, Yi Q, Eikelboom JW, et al. The effect of homocysteine lowering with B-vitamins on osteoporotic fractures in patients with cerebrovascular disease: Substudy of VITATOPS, a randomized placebo-controlled trial. *BMC Geriatr* 2013;13:88.
5. Gjertsen JE, Baste V, Fevang JM, et al. Quality of life following hip fractures; Results from the Norwegian hip fracture register. *BMC Musculoskelet Disord* 2016;17:265.

PAIN

SHORT REPORT

Tele-yoga for Chronic Pain: A Management Therapy for the Future?

By Jeffrey H. Baker, MD, FAAFP, DABMA, DABIHM

Assistant Professor, Department of Family and Community Medicine, Penn State College of Medicine, State College PA

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

SYNOPSIS: Remote video yoga instruction service has the potential to bring chronic pain improvement to those who have difficulty in accessing medical care.

Chronic pain continues to trouble people in the United States in terms of healthcare costs and lost work productivity. Mathersul et al reviewed the military's early research results in telehealth, using an innovative approach to reaching those patients who have difficulty in accessing their care. "Most days" pain is encountered more frequently in the veteran population than the general population (9.1% vs. 6.4%), whereas 65.5% of veterans reported pain in the past three months compared to 56.4% of the general population.¹ There is direct correlation of pain to the number of years of post-deployment.² Current pharmaceutical interventions have brought limited success with significant unwanted side effects. Even cognitive behavioral therapy, the standard for psychological intervention in pain therapy, has limited effectiveness. Because of the effect of chronic pain on veterans, the National Institutes of Health and the Department of Veterans Affairs have prioritized research in this field looking for other interventions that might produce results and be acceptable to patients.

As a prelude to their discussion concerning yoga and tele-yoga activities for chronic pain, the authors described "telehealth" as an inclusive term for real-time video or telephone conferencing for individuals living in remote areas or who have reduced mobility. This is in contrast to "telemedicine" that refers to direct clinical services.

Yoga is one of many mind-body or energy therapies that have been used to treat chronic pain, both as first-line and as adjunctive therapy. The authors were careful to elucidate the scenarios where in-person yoga has been studied and is helpful: cancer pain, headache, musculoskeletal pain of the lower back and neck, rheumatoid arthritis, osteoarthritis, irritable bowel syndrome, and fibromyalgia. Although in-person yoga is an effective method for treating pain, the authors suggested that telehealth sessions are feasible and may be helpful on many levels, in addition to pain management, including exercise, peer mentoring, and psychological treatments.

Suggestive evidence for support of telehealth programs comes from studies performed at the War Related Illness and Injury Study Center in Palo Alto, CA. The first study involved telehealth intervention for heart and respiratory issues in individuals with congestive heart failure and chronic obstructive pulmonary disease;³ a second study involved treating chronic pain.⁴ In these studies,

Summary Point

- Researchers reviewed the use of yoga instruction, transmitted remotely for access-challenged patients in treating chronic pain. The study suggests that tele-yoga can be an effective treatment, but it is unknown if it is as effective as in-person yoga instruction.

participants rated their satisfaction and improved self-reported pain, energy level, depression, and anxiety to be comparable to in-person yoga classes. To date for safety reasons, the Palo Alto group has not used poses that require the participant to lay prone or supine on the floor. They suggested further research will provide answers for poses that can be used safely in the telehealth mode.

The authors discussed issues that need to be addressed to further study the implementation of yoga telehealth activities. There are many differing styles of yoga that, if studied or reviewed together, would impede the identification of positive/negative effects. The addition or subtraction of mindfulness in yoga research also interferes with outcome analyses. It still is not proven that telehealth interventions are as successful as in-person interactions. Consistent study design has yet to be formulated, while the feasibility of performing large studies hinders both in-person and telehealth mind-body medicine. This article represents innovative thinking using a relatively inexpensive and accessible technology to help members of a mobile, and at times, isolated, societal group. Translation to the general population would be easy and worthwhile. We can look forward to further research from the military and integrative medical communities to aid in chronic pain management. ■

REFERENCES

1. Nahin RL. Severe pain in veterans: The effect of age and ex, and comparisons with the general population. *J Pain* 2017;18:247-254.
2. Haskell SG, Ning Y, Krebs E, et al. The prevalence of painful musculoskeletal conditions in female and male veterans in 7 years after return from deployment in Operation Enduring Freedom/Operation Iraqi Freedom. *Clin J Pain* 2012;28:163-167.
3. Selman L, McDermott K, Donesky D, et al. Appropriateness and acceptability of a tele-yoga intervention for people with heart failure and chronic obstructive pulmonary disease: Qualitative findings from a controlled pilot study. *BMC Complement Altern Medicine* 2015;2015:15-21.
4. Schulz-Heik RJ, Meyer H, Mahoney L, et al. Results from a clinical yoga program for veterans: Yoga via telehealth provides comparable satisfaction and health improvements to in-person yoga. *BMC Complement Altern Med* 2016;2016:1-9.

SHORT REPORT

Vitamin C for Postoperative Atrial Fibrillation Risk

By David Kiefer, MD, Editor

SYNOPSIS: Vitamin C supplementation decreases the risk of developing postoperative atrial fibrillation.

SOURCE: Shi R, Li ZH, Chen D, et al. Sole and combined vitamin C supplementation can prevent postoperative atrial fibrillation after cardiac surgery: A systematic review and meta-analysis of randomized controlled trials. *Clin Cardiol* 2018;41:871-878.

Vitamin C, the water soluble ubiquitous nutrient, has many purported uses, to which the overwhelming number of articles on PubMed can attest. One interesting use, as per the recent systematic review detailed here, is for postoperative atrial fibrillation. It is a compelling problem to address; the authors mentioned an incidence ranging from 17-33%, with resulting complications, even though 80% of such patients return to sinus rhythm spontaneously. With a possible mechanism of oxidative stress, it would follow that an antioxidant, such as vitamin C, might have a role in preventing atrial fibrillation postoperatively.

Shi et al identified randomized, controlled (placebo or other control) trials in adults undergoing cardiac surgery, with vitamin C either as solo therapy or as adjunctive therapy. They reviewed 13 studies involving 1,956 patients. The primary outcome was the occurrence of postoperative atrial fibrillation; the pooled analysis revealed that vitamin C supplementation reduced the incidence of atrial fibrillation (relative risk, 0.68; 95% confidence interval, 0.54-0.87; $P = 0.002$), even more so when vitamin C was added to other therapies. (See Table 1.)

Furthermore, secondary analyses revealed that vitamin C supplementation led to shorter stays in the intensive care unit, less overall time in the hospital, and a reduced risk of adverse effects (not further specified other than advice that “high-dose intake of vitamin C should be avoided”).

The authors noted that there was a “moderate” amount of heterogeneity among the studies regarding methodology and a “moderate likelihood” of publication biases as per their statistical analyses, although the power of these tests was low because of the small number of studies involved. This systematic review nudges clinicians toward using vitamin C, either alone or in combination with typical cardiac medications, after cardiac surgery.

Summary Point

- The authors of a systematic review of 13 studies found convincing evidence that vitamin C supplementation, beginning before cardiac surgery and continuing for a few days postoperatively, can decrease the risk of atrial fibrillation.

These recommendations are qualified slightly by the heterogeneity and risk of publication bias, not unheard of for systematic reviews, and possibly not a “real” issue given the small number of studies included and the effect that has on the power of the statistical methodology. Furthermore, an article of this type does not tell us how to use vitamin C, that is, in what dose or for how long. To answer those practical questions, it is necessary to look to the individual studies, where there were a variety of approaches, including a range (1,000 to 2,000 mg) of oral or intravenous doses beginning one to two days before surgery and continuing for four to five days postoperatively. ■

Table 1: Incidence (Relative Risk) of Postoperative Atrial Fibrillation When Vitamin C Supplementation Was Used Alone or in Combination With Pharmaceuticals

Vitamin C supplementation	Relative risk (95% confidence interval)	P value
All groups	0.68 (0.54-0.87)	0.002
Alone	0.75 (0.63-0.90)	0.002
With beta-blockers	0.29 (0.16-0.53)	< 0.001
With statins	0.40 (0.17-0.96)	0.040
With medications, combined	0.32 (0.20-0.53)	< 0.001

EXECUTIVE EDITOR
Leslie G. Coplin

EDITOR
Jonathan Springston

EDITORIAL GROUP MANAGER
Terrey L. Hatcher

SENIOR ACCREDITATIONS
OFFICER
Lee Landenberger

EDITOR
David Kiefer, MD
Clinical Assistant Professor, Department of
Family Medicine, University of Wisconsin;
Clinical Assistant Professor of Medicine,
Arizona Center for Integrative Medicine,
University of Arizona, Tucson

PEER REVIEWER
Suhani Bora, MD
Access Community Health Centers
Madison, WI

EDITORIAL ADVISORY BOARD
Donald Brown, ND
Managing Director
Natural Product Research Consultants
Seattle

Russell H. Greenfield, MD
Clinical Assistant Professor
School of Medicine
University of North Carolina
Chapel Hill
Visiting Assistant Professor
University of Arizona College of Medicine
Tucson

Dónal O'Mathúna, BS (Pharm), MA, PhD
Senior Lecturer
Ethics, Decision-Making & Evidence
School of Nursing and Human Sciences
Affiliated Scholar, Institute of Ethics
Dublin City University, Dublin, Ireland

David Rakel, MD
Associate Professor
Department of Family Medicine
Founder and Director, University of
Wisconsin Integrative Medicine
University of Wisconsin School of
Medicine and Public Health, Madison

Craig Schneider, MD
Director of Integrative Medicine
Department of Family Medicine
Maine Medical Center
Portland, ME

CME INSTRUCTIONS

To earn credit for this activity, please follow these instructions:

1. Read and study the activity, using the references for further research.
2. Log on to ReliasMedia.com and click on [My Account](#). First-time users must register on the site using the eight-digit subscriber number printed on the mailing label or invoice.
3. Pass the online test with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After completing the test, a credit letter will be emailed to you instantly.
5. Twice yearly after the test, your browser will be directed to an activity evaluation form, which must be completed to receive your credit letter.

CME QUESTIONS

1. **An intensive exercise program in middle-aged, sedentary but otherwise healthy participants over a two-year period demonstrated a decrease in which of the following?**
 - a. Maximum oxygen uptake
 - b. Body mass index
 - c. Diastolic blood pressure
 - d. Ventricular stiffness
2. **In patients who are at risk for hip fractures and ask about B vitamin supplementation, which of the following would be appropriate to support?**
 - a. Vitamins B12, B6, and folate
 - b. Vitamin B12
 - c. Vitamin B6
 - d. Vitamins B12 and folate
3. **Based on the results from the study by Freeman et al, which of the following is false about the relationship between sleep and mental health?**
 - a. Sleep improvement via digital cognitive behavioral therapy was linked to improvement in a variety of mental health symptoms and improvement in psychological well-being.
 - b. Paranoia and hallucinations should be treated primarily with vigorous attention to sleep.
 - c. Digital cognitive behavioral therapy in the form of Sleepio was not tested against other forms of sleep intervention.
4. **Which of the following is true regarding the use of vitamin C supplementation in people undergoing cardiac surgery?**
 - a. It is most effective at preventing atrial fibrillation when used as adjunctive therapy.
 - b. A solo therapy, it actually slightly increases the risk of atrial fibrillation.
 - c. Adverse effects are common and do not justify the minimal benefits.
 - d. Its benefits are unclear, as there are no relevant clinical trials examining this use.
5. **Telehealth studies of congestive heart failure, chronic obstructive pulmonary disease, and chronic pain have established that this form of intervention is comparable to in-person intervention.**
 - a. True
 - b. False

CME OBJECTIVES

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

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

[IN FUTURE ISSUES]

Gluten-free Diet and
Coronary Artery Disease

Acupuncture
for Infertility in Polycystic
Ovary Syndrome

Coffee and Mortality

Adaptogens for Exercise
Performance

Interested in reprints or posting an article to your company's site? There are numerous opportunities for you to leverage editorial recognition for the benefit of your brand.
Call us: (800) 688-2421
Email us: reprints@reliamedia.com

For pricing on group discounts, multiple copies, site-licenses, or electronic distribution, please contact our Group Account Managers at:

Phone: (866) 213-0844
Email: groups@reliamedia.com

To reproduce any part of Relias newsletters for educational purposes, please contact:

The Copyright Clearance Center for permission
Email: info@copyright.com
Phone: (978) 750-8400