InspireHealth
INTEGRATIVE CANCER CARE

# RESEARCH UPDATES JUNE 2014

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**FOR THE LATEST IN WORLDWIDE INTEGRATIVE CANCER CARE**

**IN THIS ISSUE:** In their retrospective study, Zelenskiy et al. found that a high glycemic load diet was associated with increased colon cancer risk. Link and colleagues found that a plant-based diet high in fruits and vegetables was associated with reduced risk of breast cancer. Gardner and colleagues reviewed exercise intervention studies in men undergoing androgen-deprivation therapy and found that exercise improved fatigue, chronic disease risk factors, and quality of life. Bower et al. found that 12 weeks of restorative yoga practice reduced inflammatory markers in breast cancer survivors with persistent fatigue. Garland and associates found that cognitive behavioural therapy was superior to mindfulness-based stress reduction for the treatment of insomnia in Canadian cancer patients. Holmes and associates found that compared to those who exercised for less than 1 hour/week, breast cancer patients who exercised more than 3 hours/week had significantly reduced risk of both breast cancer recurrence and death from any cause.

## NUTRITION

Zelenskiy, S, C. L. Thompson, T. C. Tucker, et al.

### High Dietary Glycemic Load is Associated with Increased Risk of Colon Cancer.

*Nutr Cancer.* 2014 03 Apr 2014; 663: 362-368.

High dietary glycemic load (GL) has been inconsistently associated with risk of colon cancer. We analyzed data for 1093 incident cases and 1589 controls in a population-based case-control study of colon cancer to further clarify the GL-colon cancer relationship. GL was assessed using a self-administered food frequency questionnaire. Cases had a significantly higher GL intake (mean = 136.4, SD = 24.5) than controls (mean = 132.8, SD = 25.2) (P = 0.0003). In a multivariate unconditional logistic regression model, the odds ratios (ORs) for colon cancer increased significantly with increasing GL: compared to the bottom quartile of GL, the ORs (95% CI) for the 2nd through the upper quartiles were 1.38 (1.06, 1.80), 1.67 (1.30, 2.13), and 1.61 (1.25, 2.07), respectively (P trend < 0.0001). Stratified analyses showed that the association was more pronounced among older participants [ORs (95% CI) for the 2nd through the upper quartiles were 1.35 (0.91, 2.00), 1.87 (1.29, 2.71), 2.02 (1.39, 2.95), respectively] than among younger participants [ORs were 1.46 (1.02, 2.10), 1.53 (1.09, 2.15), and 1.35 (0.96, 1.91), respectively] (P int = 0.02). Our results provide support for the hypothesis that a diet with high GL increases the risk of colon cancer.

**INSPIREHEALTH'S INTERPRETATION:** Glycemic load is a measure of the expected rise in blood glucose after food consumption. It is determined by both the food's carbohydrate content, and by how quickly that carbohydrate is absorbed in the body. A rise in blood glucose is usually followed by a rise in insulin and insulin-like growth factors (IGFs). Several authors have proposed relationships between a diet high in energy and carbohydrates and colon carcinogenesis. However, reviews that investigated glycemic load and colorectal cancer have produced mixed results. This retrospective observational study aimed to further investigate dietary glycemic load and the risk of colon cancer. From 2003-2010, 1093 newly diagnosed colon cancer patients in the Kentucky area participated in the study. Patients filled out a questionnaire that assessed dietary information and other lifestyle factors during the year prior to cancer diagnosis. Data from this group were then compared to a control group. Participants in the control group were not diagnosed with cancer (except non-melanoma skin cancer) and were recruited via random digit phone calls.

After controlling for total energy intake, fiber intake, vitamin D intake, body mass index, physical activity, income, and smoking, significant differences were found between the colon cancer patients and controls. Overall, those who consumed the highest glycemic load diet had a 67% increased risk of colon cancer compared to those who consumed the lowest glycemic load diet.

Risk of colon cancer doubled for those who consumed the highest glycemic load diet and were older than 63 years of age, compared to the lowest glycemic load consumers of the same age. Interestingly, an association between glycemic load and colon cancer risk was found between healthy-weight and vigorously active individuals. This shows that even if your body weight is deemed 'normal' and you are physically active, eating well is still important. However, specific associations in this study should be interpreted with caution. Diet was only assessed for the single year immediately before cancer diagnosis. Cancer development takes time and perhaps diet throughout one's life has a greater impact on cancer development than in the single year before diagnosis. Additionally, the retrospective nature of this study means that participants provided dietary history based on memory. Thus the data may be vulnerable to recall bias. Despite its limitations, this study provides evidence that a dietary pattern, rather than a specific food itself, may increase risk of colon cancer.

## NUTRITION

Link, LB, A. J. Canchola, L. Bernstein, et al.

### Dietary Patterns and Breast Cancer Risk in the California Teachers Study Cohort.

*Am J Clin Nutr.* 2013 Dec; 986: 1524-1532.

**BACKGROUND:** Evidence that diet is associated with breast cancer risk is inconsistent. Most studies have examined risks associated with specific foods and nutrients, rather than measures of overall diet. **OBJECTIVE:** This study aimed to evaluate dietary patterns and their relation to breast cancer risk in a large cohort of women. **DESIGN:** Data from 91,779 women in the California Teachers Study cohort were analyzed, including data from 4140 women with a diagnosis of invasive breast cancer made between 1995 and 2009. Five predominant dietary patterns were identified by using principal components factor analysis: a plant-based diet, high in fruit and vegetables; a high-protein, high-fat diet, high in meats, eggs, fried foods, and high-fat condiments; a high-carbohydrate diet, high in convenience foods, pasta, and bread products; an ethnic diet, high in legumes, soy-based foods, rice, and dark-green leafy vegetables; and a salad and wine diet, high in lettuce, fish, wine, low-fat salad dressing, and coffee and tea. **RESULTS:** The plant-based pattern was associated with a reduction in breast cancer risk (RR: 0.85; 95% CI: 0.76, 0.95 for the highest compared with the lowest consumption quintile; P-trend = 0.003); risk reduction was greater for estrogen receptor-negative progesterone receptor-negative (ER-PR-) tumors (RR: 0.66; 95% CI: 0.48, 0.91; P-trend = 0.03). The salad and wine pattern was associated with an increased risk of estrogen receptor-positive progesterone receptor-positive tumors (RR: 1.29; 95% CI: 1.12, 1.49); this effect was only slightly attenuated after adjustment for alcohol consumption. **CONCLUSION:** The finding that greater consumption of a plant-based dietary pattern is associated with a reduced breast cancer risk, particularly for ER-PR- tumors, offers a potential avenue for prevention.

**INSPIREHEALTH'S INTERPRETATION:** Many people want to make healthful dietary changes to reduce their risk of cancer or a cancer recurrence. Unfortunately, research examining links between diet and cancer are often fraught with methodological challenges making it difficult to obtain accurate and relevant information. Dietary intake can be difficult for participants to accurately recall and the interactions between various nutrients are so complex that analysis focusing on individual foods and nutrients compared to measures of overall diet may lead to erroneous associations. In this well designed, large prospective cohort study, 91,979 women who had completed a questionnaire regarding personal and lifestyle characteristics such as reproductive history, use of estrogen/vitamins/medications, medical history, personal and family history of cancer, exercise, dietary intake and alcohol and tobacco use were followed for approximately 15 years for the development of cancer. During the study period 4140 women developed breast cancer.

Five predominant dietary patterns were identified: plant-based (high in fruits and vegetables), high protein/high fat (high in meats, eggs, fried foods, fatty condiments), carbohydrate rich (high in convenience foods, pasta, breads), ethnic (high in legumes, soy-based foods, rice, dark-green leafy vegetables) and salad and wine (high in lettuce, fish, wine, low-fat dressing, coffee, tea). Only two dietary patterns emerged as having an association with the development of breast cancer. Women with the highest versus the lowest consumption of a plant-based diet had a 15% reduced risk of developing breast cancer; for women whose breast cancers were estrogen and progesterone receptor (ER and PR) negative there was a 34% reduced risk. Women with the highest versus the lowest consumption of a salad and wine diet had an overall 12% increased risk of developing breast cancer, but a 29% increased risk for developing ER+/PR+ breast cancers. Adjustments for alcohol intake in the salad and wine diet only reduced the increased risk from 12% to 9%, suggesting that alcohol consumption did not account for the observed association. Additionally, use of post-menopausal hormone therapy (thought to be associated with increased risk of breast cancer) was more prevalent among women who consumed the salad and wine diet, perhaps accounting for some the observed association.

The findings of this study are consistent with many other observational studies showing that a plant-based diet may protect against the development of breast cancer. There are many possible explanations for the above results. First, plants contain

antioxidants and phytochemicals, many of which have been shown in-vitro, and in some cases in-vivo to inhibit or reduce cancer cell growth. Second, some plants have high levels of insoluble fibre which binds estrogen increasing its excretion to reduce circulating levels. Third, diets high in fibre tend to be lower in glycemic load which has been associated with reduced cancer risk. InspireHealth recommends a diet rich in plant-based foods supplemented with appropriate quantities of high quality healthy grains, fats, and proteins for maximal exposure to a variety of healthy nutrients.

## ANDROGEN-DEPRIVATION THERAPY

Gardner, JR, P. M. Livingston and S. F. Fraser.

### Effects of Exercise on Treatment-Related Adverse Effects for Patients with Prostate Cancer Receiving Androgen-Deprivation Therapy: A Systematic Review.

*Journal of Clinical Oncology.* 2014 Feb 1; 324: 335-346.

**PURPOSE:** Androgen-deprivation therapy is a commonly used treatment for men with prostate cancer; however, the adverse effects can be detrimental to patient health and quality of life. Exercise has been proposed as a strategy for ameliorating a range of these treatment-related adverse effects. We conducted a systematic review of the literature regarding the effects of exercise on treatment-related adverse effects in men receiving androgen-deprivation therapy for prostate cancer. **METHODS:** An online electronic search of the Cochrane Library, EMBASE, MEDLINE, CINAHL, SPORTDiscus, and Health Source databases was performed to identify relevant peer-reviewed articles published between January 1980 and June 2013. Eligible study designs included randomized controlled trials as well as uncontrolled trials with pre- and postintervention data. Information was extracted regarding participant and exercise intervention characteristics as well as the effects of exercise on bone health, body composition, physical performance, cardiometabolic risk, fatigue, and quality of life. **RESULTS:** Ten studies were included, with exercise interventions involving aerobic and/or resistance training. Exercise training demonstrated benefits in muscular strength, cardiorespiratory fitness, functional task performance, lean body mass, and fatigue, with inconsistent effects observed for adiposity. The impact of exercise on bone health, cardiometabolic risk markers, and quality of life are currently unclear. **CONCLUSION:** Among patients with prostate cancer treated with androgen-deprivation therapy, appropriately prescribed exercise is safe and may ameliorate a range of treatment-induced adverse effects. Ongoing research of high methodologic quality is required to consolidate and expand on current knowledge and to allow the development of specific evidence-based exercise prescription recommendations.

**INSPIREHEALTH'S INTERPRETATION:** Hormone therapy, also called androgen deprivation therapy (ADT) or anti-androgen therapy is commonly used in prostate cancer treatment. Although ADT has been shown to slow tumour progression and improve survival in some men, it has significant negative side effects (e.g. reduced libido, loss of muscle mass, increased fatty tissue, hot flashes, mood lability, osteoporosis, and anemia) which can affect patients' health and quality of life. In this study, the authors searched the literature for studies examining the role of exercise in treating the adverse effects of ADT. Intervention studies were eligible for review if they involved prescribed aerobic and/or resistance training and measured outcomes such as physical and psychological health, and quality of life (QOL). A total of 14 good quality studies providing data from 10 exercise intervention trials met the inclusion criteria and were examined in detail. Most studies included an average of 3 exercise sessions per week for 12 weeks.

Results showed that exercise training improved physical performance as measured by increased cardiorespiratory fitness, muscular strength and endurance, as well as everyday task completion. Interestingly, the benefits gained by the ADT treated men reflected those observed elsewhere in otherwise healthy older adults. Improvements in fatigue and even some protection against anemia (low hemoglobin) were noted. Effects of exercise on QOL, bone health, and cardiometabolic risk factors such as blood lipids and blood glucose levels showed either benefit or no change. Certainly, exercise did not worsen outcomes, and it is possible that if the exercise interventions had been of longer duration, frequency, and/or greater intensity more consistent positive outcomes might have been found. Importantly, the exercise programs were well tolerated by the patients and did not reduce ADT efficacy.

The authors conclude that patients should aim for 30 minutes of moderate intensity aerobic activity 3-5 times/week and add resistance training 1-3 times/week. These recommendations echo those of InspireHealth though we like to remind members that exercise is not an all or nothing phenomenon. For those undergoing treatment or for whom fatigue is a significant issue, even getting outside for a slow 5-10 minute walk can provide benefit.

## YOGA

Bower JE, G Greendale, A.D. Crosswell, et al.

### Yoga Reduces Inflammatory Signaling in Fatigued Breast Cancer Survivors: A Randomized Controlled Trial.

*Psychoneuroendocrinology.* 2014 May; 43:20-9.

**BACKGROUND:** Yoga is a popular mind-body therapy that has demonstrated beneficial effects on psychological, behavioral, and functional outcomes. However, few studies have investigated effects on inflammatory processes. This study tested the hypothesis that an Iyengar yoga intervention specifically designed for fatigued breast cancer survivors would lead to decreases in inflammation-related gene expression and circulating markers of proinflammatory cytokine activity. **METHODS:** Breast cancer survivors with persistent cancer-related fatigue were randomized to a 12-week Iyengar yoga intervention (n=16) or a 12-week health education control condition (n=15). Blood samples were collected at baseline, post-intervention, and at a 3-month follow-up for genome-wide transcriptional profiling and bioinformatic analyses. Plasma inflammatory markers and salivary cortisol were also assessed. **RESULTS:** In promoter-based bioinformatics analyses, the yoga group showed reduced activity of the pro-inflammatory transcription factor nuclear factor kappa B (NF-κB), increased activity of the anti-inflammatory glucocorticoid receptor, and reduced activity of cAMP response element-binding protein (CREB) family transcription factors relative to controls (all ps<.05). There was also a significant intervention effect on the soluble tumor necrosis factor receptor type II (sTNF-RII), a marker of TNF activity; plasma levels of sTNF-RII remained stable in the yoga group, whereas levels of this marker increased in the health education group (p=.028). A similar, non-significant trend was observed for the interleukin 1 receptor antagonist (p=.16). No significant changes in C reactive protein (CRP), interleukin 6 (IL-6), or diurnal cortisol measures were observed. **CONCLUSIONS:** A 12-week restorative Iyengar yoga intervention reduced inflammation-related gene expression in breast cancer survivors with persistent fatigue. These findings suggest that a targeted yoga program may have beneficial effects on inflammatory activity in this patient population, with potential relevance for behavioral and physical health.

**INSPIREHEALTH'S INTERPRETATION:** In clinical settings, yoga is often used for therapeutic purposes; however its direct physiological effects on inflammation are still unclear. Inflammation has been associated with cancer development as well as a host of other chronic illnesses. This randomized controlled trial looked at the effects of a 12-week restorative Iyengar yoga program on cortisol levels (a hormone normally elevated during stress), and pro-inflammatory transcription factors (NF-κB, CREB, ISRE) in breast cancer survivors. This study is interesting because these researchers measured physiological changes in biological markers of inflammation and gene expression following the yoga intervention instead of relying on self-reported data from questionnaires. Thirty-one patients were randomized (flip-a-coin) into either the 12-week yoga program or a 12-week health education program. Following the intervention, cortisol levels were unchanged in both groups.

However, the highlights of this study are the changes observed in biochemical pathways that influence inflammation. Patients who participated in the yoga program had significantly reduced circulating levels of the transcription factors NF-κB, CREB, and ISRE. Transcription factors regulate gene expression by signaling a cell to produce specific proteins. NF-κB, CREB, and ISRE largely affect gene expression in immune cells. By reducing the circulating levels of pro-inflammatory transcription factors, cells will produce fewer pro-inflammatory proteins. With a small number of participants, this study serves as a preliminary investigation into the effects of yoga on inflammatory processes within the body. InspireHealth offers yoga classes to cancer patients and cancer survivors as part of its therapeutic services.

## INSOMNIA

Garland, SN, L. E. Carlson, A. J. Stephens, et al.

### Mindfulness-Based Stress Reduction Compared with Cognitive Behavioral Therapy for the Treatment of Insomnia Comorbid with Cancer: A Randomized, Partially Blinded, Noninferiority Trial.

*Journal of Clinical Oncology.* 2014 Feb 10; 325: 449-457.

**PURPOSE:** Our study examined whether mindfulness-based stress reduction (MBSR) is noninferior to cognitive behavioral therapy for insomnia (CBT-I) for the treatment of insomnia in patients with cancer. **PATIENTS AND METHODS:** This was a randomized, partially blinded, noninferiority trial involving patients with cancer with insomnia recruited from a tertiary cancer center in Calgary, Alberta, Canada, from September 2008 to March 2011. Assessments were conducted at baseline, after the program, and after 3 months of follow-up. The noninferiority margin was 4 points measured by the Insomnia Severity Index. Sleep diaries and actigraphy measured sleep onset latency (SOL), wake after sleep onset (WASO), total sleep time (TST), and sleep efficiency. Secondary outcomes included sleep quality, sleep beliefs, mood, and stress. **RESULTS:** Of 327 patients screened, 111 were randomly assigned (CBT-I, n = 47; MBSR, n = 64). MBSR was inferior to CBT-I for improving insomnia

severity immediately after the program (P = .35), but MBSR demonstrated noninferiority at follow-up (P = .02). Sleep diary-measured SOL was reduced by 22 minutes in the CBT-I group and by 14 minutes in the MBSR group at follow-up. Similar reductions in WASO were observed for both groups. TST increased by 0.60 hours for CBT-I and 0.75 hours for MBSR. CBT-I improved sleep quality (P < .001) and dysfunctional sleep beliefs (P < .001), whereas both groups experienced reduced stress (P < .001) and mood disturbance (P < .001). **CONCLUSION:** Although MBSR produced a clinically significant change in sleep and psychological outcomes, CBT-I was associated with rapid and durable improvement and remains the best choice for the nonpharmacologic treatment of insomnia.

**INSPIREHEALTH'S INTERPRETATION:** Noninferiority trials are done to determine whether or not a new treatment is as good as (not-inferior-to) an accepted treatment for a given condition or set of symptoms. In this case, the accepted treatment for insomnia is cognitive behavioural therapy (CBT-I), and the treatment being compared is mindfulness-based stress reduction (MBSR). CBT addresses emotions and behavioural dysfunction through goal-oriented methods and MBSR is a method of mindful awareness that includes techniques such as meditation, yoga, and awareness of the present moment. Estimates suggest that 21% to 28% of cancer patients meet requirements for a formal insomnia diagnosis during or after treatment, and that up to 59% experience some disturbed sleep and insomnia symptoms. Patients for this study were recruited from a cancer centre in Calgary, Alberta and were partially blinded to the study design so that they only had knowledge of the treatment arm they completed. Measurements included insomnia severity, sleep quality (measured both subjectively and objectively), and psychological outcomes (stress, mood, and attitude towards sleep). Patients randomized into the CBT-I group received 12 hours of instruction over 8 weekly sessions, while those randomized into the MBSR group received 18 hours of instruction over 8 weekly sessions, plus one 6 hour silent retreat.

Patients were assessed in the above categories at baseline, after the intervention, and 3 months after that. Following the intervention, insomnia severity was lower in the CBT-I group, however by the follow-up assessment there was no difference between groups. Total sleep time improved in both groups, however sleep efficiency (measured with sleep monitoring) was only improved in the CBT-I group. Though both the CBT-I and MBSR groups experienced significant improvements in sleep quality, sleep beliefs, and stress, the CBT-I group was superior for improvements in sleep quality and sleep beliefs. Overall, MBSR was as good as CBT-I for reducing insomnia severity, however CBT-I outperformed MBSR in both subjective and objective sleep quality measures, and did so immediately following the intervention.

## INTO THE VAULT

Holmes MD, W. Y. Chen, D. Feskanich, et al.

### Physical Activity and Survival After Breast Cancer Diagnosis.

*JAMA.* 2005 May 25; 293(20): 2479-86.

**CONTEXT:** Physical activity has been shown to decrease the incidence of breast cancer, but the effect on recurrence or survival after a breast cancer diagnosis is not known. **OBJECTIVE:** To determine whether physical activity among women with breast cancer decreases their risk of death from breast cancer compared with more sedentary women. **DESIGN, SETTING, AND PARTICIPANTS:** Prospective observational study based on responses from 2987 female registered nurses in the Nurses' Health Study who were diagnosed with stage I, II, or III breast cancer between 1984 and 1998 and who were followed up until death or June 2002, whichever came first. **MAIN OUTCOME MEASURE:** Breast cancer mortality risk according to physical activity category (<3, 3-8.9, 9-14.9, 15-23.9, or > or =24 metabolic equivalent task [MET] hours per week). **RESULTS:** Compared with women who engaged in less than 3 MET-hours per week of physical activity, the adjusted relative risk (RR) of death from breast cancer was 0.80 (95% confidence interval [CI], 0.60-1.06) for 3 to 8.9 MET-hours per week; 0.50 (95% CI, 0.31-0.82) for 9 to 14.9 MET-hours per week; 0.56 (95% CI, 0.38-0.84) for 15 to 23.9 MET-hours per week; and 0.60 (95% CI, 0.40-0.89) for 24 or more MET-hours per week (P for trend = .004). Three MET-hours is equivalent to walking at average pace of 2 to 2.9 mph for 1 hour. The benefit of physical activity was particularly apparent among women with hormone-responsive tumors. The RR of breast cancer death for women with hormone-responsive tumors who engaged in 9 or more MET-hours per week of activity compared with women with hormone-responsive tumors who engaged in less than 9 MET-hours per week was 0.50 (95% CI, 0.34-0.74). Compared with women who engaged in less than 3 MET-hours per week of activity, the absolute unadjusted mortality risk reduction was 6% at 10 years for women who engaged in 9 or more MET-hours per week. **CONCLUSIONS:** Physical activity after a breast cancer diagnosis may reduce the risk of death from this disease. The greatest benefit occurred in women who performed the equivalent of walking 3 to 5 hours per week at an average pace, with little evidence of a correlation between increased benefit and greater energy expenditure. Women with breast cancer who follow US physical activity recommendations may improve their survival.

**INSPIREHEALTH'S INTERPRETATION:** This 2005 prospective observational study examined the relationship between increasing amounts of exercise and breast cancer survival and recurrence. In their introduction, the authors state that higher

physical activity levels are associated with lower levels of circulating ovarian hormones (estrogen, progesterone) and that this relationship might be one of the reasons exercise is beneficial for breast cancer patients. The Nurses' Health Study (which began in 1976) included 2987 women with stage 1, 2, or 3 breast cancer. Each patient's physical activity was quantified by a bi-annual questionnaire which asked the question "During the past year, what was your average time spent per week at each of several activities (e.g. walking, running, tennis, bicycling, swimming, aerobics, and others)?" Patients were followed until death, recurrence of breast cancer, or until the end of the study in 2004 and then put into one of five categories based on their average time spent exercising: <1, 1-3, 3-5, 5-8, or >8 hours per week (at the equivalent intensity to walking at 3.2-4.7 Km/h).

Patients who exercised 3-5 hours per week had a 50% reduced risk of death from breast cancer, and a 43% reduced risk of recurrence compared to patients who exercised for less than 1 hour per week. Exercising more than 3-5 hours per week did not provide additional risk reduction. In further analysis, the authors found that if patients were split into just two groups - those who exercised less than 3 hours per week and those who exercised more than 3 hours per week – the beneficial association held true, especially for patients with a stage 3 diagnosis. Compared to stage 3 patients who exercised less than 3 hours per week, stage 3 patients who exercised more than 3 hours per week had a 64% reduced risk of death by any cause. Additionally, the authors looked at the effects of more vigorous exercise and found a similar reduction in mortality risk in patients who had more than 2.5 hours of vigorous exercise per week compared to patients who had none.

The data from this study suggest that after achieving a certain amount of exercise per week, more exercise was not associated with further risk reductions in mortality and recurrence. Walking or participating in other types of physical activity for 30 minutes every day amounts to 3.5 hours of exercise/week, and may significantly reduce risk of death and cancer recurrence. Such a program serves as an example and is not the only way to achieve your weekly exercise goal. Some days may include longer bouts or more intense exercise balanced with rest days in between to give your body a chance to recover. As well, proper nutrition is important when exercising regularly. As a general rule, it is good to eat a healthy meal that includes protein and complex carbohydrates within an hour of exercising. InspireHealth offers in-person and online exercise therapy appointments to help you determine the appropriate amount and type of exercise to support you through your journey.

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