Headache
© 2015 American Headache Society
ISSN 0017-8748
doi: 10.1111/head.12738
Published by Wiley Periodicals, Inc.

Views and Perspectives

Aerobic Exercise for Reducing Migraine Burden: Mechanisms, Markers, and Models of Change Processes

Megan B. Irby, MS, MS; Dale S. Bond, PhD; Richard B. Lipton, MD; Barbara Nicklas, PhD; Timothy T. Houle, PhD; Donald B. Penzien, PhD

Background.—Engagement in regular exercise routinely is recommended as an intervention for managing and preventing migraine, and yet empirical support is far from definitive. We possess at best a weak understanding of how aerobic exercise and resulting change in aerobic capacity influence migraine, let alone the optimal parameters for exercise regimens as migraine therapy (eg, who will benefit, when to prescribe, optimal types, and doses/intensities of exercise, level of anticipated benefit). These fundamental knowledge gaps critically limit our capacity to deploy exercise as an intervention for migraine.

Overview.—Clear articulation of the markers and mechanisms through which aerobic exercise confers benefits for migraine would prove invaluable and could yield insights on migraine pathophysiology. Neurovascular and neuroinflammatory pathways, including an effect on obesity or adiposity, are obvious candidates for study given their role both in migraine as well as the changes known to accrue with regular exercise. In addition to these biological pathways, improvements in aerobic fitness and migraine alike also are mediated by changes in psychological and sociocognitive factors. Indeed a number of specific mechanisms and pathways likely are operational in the relationship between exercise and migraine improvement, and it remains to be established whether these pathways operate in parallel or synergistically. As heuristics that might conceptually benefit our research programs here forward, we: (1) provide an extensive listing of potential mechanisms and markers that could account for the effects of aerobic exercise on migraine and are worthy of empirical exploration and (2) present two exemplar conceptual models depicting pathways through which exercise may serve to reduce the burden of migraine.

Conclusion.—Should the promise of aerobic exercise as a feasible and effective migraine therapy be realized, this line of endeavor stands to benefit migraineurs (including the many who presently remain suboptimally treated) by providing a new therapeutic avenue as an alternative or augmentative compliment to established interventions for migraine.

Key words: migraine, aerobic exercise, self-management, self-efficacy, outcome expectancies, aerobic fitness, self-regulation, endocannabinoids, inflammation

From the Department of Anesthesiology, Wake Forest School of Medicine, Winston-Salem, NC, USA (M.B. Irby, T.T. Houle, and D.B. Penzien); Department of Pediatrics, Brenner FIT, Wake Forest School of Medicine, Winston-Salem, NC, USA (M.B. Irby); Department of Psychiatry and Human Behavior, Alpert Medical School of Brown University/The Miriam Hospital Weight Control and Diabetes Research Center, Providence, RI, USA (D.S. Bond); Department of Neurology, Montefiore Headache Center, Albert Einstein College of Medicine, Bronx, NY, USA (R.B. Lipton); Department of Gerontology and Geriatric Medicine, Center for Genomics and Personalized Medicine Research, Wake Forest School of Medicine, Winston-Salem, NC, USA (B. Nicklas); Department of Neurology, Wake Forest School of Medicine, Winston-Salem, NC, USA (T.T. Houle).

Address all correspondence to Megan B. Irby, Department of Anesthesiology, Wake Forest School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157, USA, email: mirby@wakehealth.edu

Accepted for publication October 16, 2015.

Conflict of Interest: Megan B. Irby, Dale S. Bond, and Barbara Nicklas declare no potential conflicts of interest. Richard B. Lipton holds stock options in eNeura Therapeutics, and he serves as consultant, advisory board member, or has received honoraria from: Allergan, American Headache Society, Autonomic Technologies, Boston Scientific, Bristol Myers Squibb, Cognimed, Colucid, Eli Lilly & Company, Endo, eNeura Therapeutics, Merk & Co., Inc., Novartis, NuPathe, Pfizer, and Teva, Inc. Timothy T. Houle and Donald B. Penzien have received research support from Merck & Co., Inc.

Abbreviations: HRQoL health-related quality of life, ICHD International Classification of Headache Disorders, CGRP calcitonin gene-related peptide, BDNF brain-derived neurotrophic factor, CRP C-reactive protein, TNF-α tumor necrosis factor-α, IL-6 interleukin-6

(*Headache* 2015;00:00-00)

INTRODUCTION

Habitual aerobic exercise (ie, activities that utilize large muscle groups repetitively and maintain an increased heart rate for sustained periods of time) can prevent or reduce symptoms of several chronic diseases and medical conditions. Aerobic exercise may seem a well-established therapeutic avenue for reducing migraine burden. As evidence, numerous major health and medical organizations recommend that patients engage in regular exercise as a means of managing and preventing migraine (eg, the American Academy of Neurology, American College of Physicians, American Headache Society, and the National Institute of Neurological Disorders and Stroke). While there is some empirical support for this recommendation, the extant research is far from definitive. We lack answers to the most fundamental questions regarding the relationship between aerobic exercise and migraine: (1) Which individuals with migraine benefit most from exercise?; (2) Is there an exercise-migraine relief dose response curve?; (3) Can exercise precipitate a migraine attack, and if so, why and can this be prevented?; (4) What types and intensities of aerobic exercise are optimal?; (5) Is aerobic exercise an effective primary treatment?; (6) Are the benefits of aerobic exercise synergistic with other behavioral or pharmacologic interventions?'; and (7) What mechanisms (biological, psychological) underlie the potential efficacy of aerobic exercise as a treatment for migraine?

We recently conducted a systematic review that revealed headache interventions incorporating aerobic exercise can yield at least modestly beneficial outcomes for migraine (total n = 9 studies).[1] Virtually all of the studies reported reductions in headache frequency and/or intensity. Seven of nine studies reported improvements in at least one secondary outcome (health related quality of life (HRQoL, n = 3; disability, n = 3; depression, n = 5), and no study reporting worsening of migraine. Despite the apparent consistency in these findings, it is a challenge to draw conclusions about the independent effects of exercise as most published reports to date (and all studies reviewed by Baillie et al[1]) have examined exercise as only one element of multicomponent migraine interventions. Published data also are less than definitive in that only two of nine studies Baillie et al[1] reviewed were randomized, controlled trials, and exercise varied among studies in type, frequency duration and intensity. Earlier reviewers[2] were similarly critical of this literature's methodology, reporting the recommendation for exercise as a migraine treatment deserved a grade of only B-C (based on evidence-based medicine principles: no randomized, controlled trials; evidence dawn from individual cohort studies, outcomes research, and case–control studies). Despite these methodological limitations, available evidence from the few trials in which aerobic exercise was the primary intervention for migraine headache activity reveals a mean reduction in headache frequency of approximately 40% at posttreatment,[3-6] suggesting that exercise as a sole intervention may yield headache improvement on par with established behavioral and pharmacological interventions for migraine.

Thus, much remains to be learned regarding the specific effects of aerobic exercise on migraine, and there is a great deal more yet to be explored regarding the physiologic and psychological mechanisms in aerobic exercise that play a role in improving migraine activity. Fortunately a number of valuable insights can be gleaned from one of the better trials to date.[7] In their 3-group randomized, controlled trial, Varkey et al[7] compared aerobic exercise with topiramate or relaxation training. All three interventions proved beneficial and equivalent

with respect to their primary outcome variable (number of headache attacks). Adverse events were not reported in the aerobic exercise or relaxation training groups but occurred in one-third of patients in the topiramate group. Study attrition rates were low for exercise (16%), relaxation training (13%), and higher for topiramate (32%). Predictably, maximal oxygen intake significantly increased for the exercise group only. While we find considerable value in this work, we concur with Ahn[8] in his assertion that Varkey et al's[7] results are generalizable only to persons with 2-8 migraine days per month. Differential benefits by treatment group might have emerged if persons with more frequent or severe migraine had been enrolled.

Even in the absence of definitive research, a prescription of aerobic exercise may be well advised for migraineurs. There is suggestive evidence that exercise is beneficial for migraine, as it can confer multiple health benefits (eg, improvements in weight management, sleep regulation, mood, cardiovascular function) without causing harm or side effects. Exercise also proves beneficial in the management of multiple other conditions that frequently are comorbid with migraine (eg, obesity, hypertension, dyslipidemia, sleep apnea, depression, anxiety).[9-12]

It may prove worthwhile to examine parallels between the exercise and depression literature versus the exercise and migraine literature. For example, as in the migraine/exercise arena, experiential evidence gleaned over the last 30 years consistently was interpreted as linking exercise with improvements in mental health outcomes. However, research empirically establishing the efficacy of exercise as a viable intervention for clinical populations diagnosed with depression remained relatively absent until the last decade.[13] There now exists substantial empirical evidence boasting the antidepressive effect of exercise, with significant improvements in depressive symptoms equal to or better than antidepressant drugs alone.[14] Though antidepressant medications may facilitate more rapid therapeutic responses, an aerobic exercise training program of the appropriate frequency, intensity, and duration can be equally effective for reducing depression in adults.[14,15] As such, adequate doses (45-60 minutes) of regular (3-5 days per week), moderate-to-vigorous (50-85% of maximum heart rate) aerobic exercise may be considered an alternative to pharmaceutical therapies, with noticeable benefits in as little as four weeks. Unfortunately, the evidence-base definitively establishing the value of exercise as a viable intervention for clinical populations with migraine is still nascent.

This body of literature addressing exercise and depression also may be particularly helpful for elucidating potential mechanisms linking exercise and migraine improvement, as the anti-depressive effect of exercise may well be conferred through similar biological and psychological mechanisms, and certain antidepressant medications have shown success in reducing migraine frequency and severity.[16,17] Studies thus far have shown that the therapeutic effect of aerobic activity on depression may be mediated through enhanced endorphin levels and neurotransmitter function,[18] improved hormone regulation,[19] decreased inflammation,[20] and, like antidepressants, increased serotonergic activation and neurogenesis.[18,21] Improvements in self-efficacy and self-esteem also are associated with improvements in symptoms of both depression[22-24] and migraine.[25] As it pertains to migraine, the progress documented over the last three decades in the exercise and depression literature provides an excellent model for determining effective guidelines for exercise as a migraine therapy.

Moreover, an exercise intervention may prove well-suited for migraineurs given their tendency toward inactivity[26-29] and the reported linear association between low physical activity and greater migraine frequency.[30] Unfortunately, the available evidence sheds no light on whether migraine contributes to low levels of physical activity or vice versa, and there is conflicting evidence on whether migraine is a barrier to exercise participation; perhaps fear that exercise may trigger and/or exacerbate headaches leads to reduced activity.[31-33] Despite the ancillary advantages, it is nevertheless essential to develop an evidence base addressing

the specific effects of exercise on migraine itself in order to optimize treatment recommendations.

Does exercise trigger migraine? This a reasonable question given that exacerbation of headache by physical activity is a defining diagnostic feature of migraine according to the ICHD.[34] The ICHD criteria list *exacerbation* of headache episodes by physical activity/exercise as a cardinal feature of migraine – not the *triggering* of headache. In contrast with migraine, physical activity/exercise serves as a trigger for *Primary Exercise Headache* (ICHD 4.2).[34-36] Nevertheless, some migraineurs believe that exercise can trigger migraine. For example, retrospective surveys have suggested between 22% and 38% of patients report a lifetime history of at least one exercise-triggered migraine attack.[37,38] But the latter findings may have been influenced by recall bias as evidence from laboratory and intervention trials does not support the assertion that exercise-induced headache applies to the typical migraineur.[29] In published trials prospectively examining aerobic exercise as a treatment for migraine, there have been few reports of exercise-induced headache. For example, Varkey et al reported a 0.1% incidence of migraine occurring in proximity to exercise in one trial,[30] and reported no adverse headache events in a later trial.[7] In future investigations it would be prudent to track and report incidence of migraine in proximity to exercise. Interestingly, although "exacerbation of headache by physical activity" is incorporated into the ICHD criteria for migraine, a recent study by Bond et al[28] found no association between objectively measured daily physical activity and how often physical activity was cited as an exacerbating factor in migraine attacks during a 4-week diary assessment. Therefore, and contrary to popular belief, physical activity may not play an important role in triggering or exacerbating migraine.

Mechanisms and Markers.—If aerobic exercise demonstrably reduces the frequency, duration, severity or associated disability of migraine, then we must articulate the mechanisms and pathways that confer these benefits. These insights could inform the development of optimal exercise programs and shed light on the pathophysiology of migraine.

Perhaps the most common mechanistic conceptualization implies that aerobic exercise confers its benefit on migraine via exercise-induced enhancements in aerobic fitness. This conceptualization is broad as the benefits of increased aerobic fitness could be mediated by any number of cardiopulmonary, inflammatory, and neurovascular processes. As a neurovascular and neuroinflammatory disorder, the physiology of migraine overlaps with the physiology of aerobic fitness in multiple ways.[39] Beyond biological pathways, improvements in aerobic fitness and migraine may be mediated by overlapping changes in sociocognitive factors, such as self-efficacy beliefs and outcome expectations for both exercise participation and migraine self-management.[40,41] In reality, there are a number of specific mechanisms and pathways that potentially could be operational in the relationship between exercise and migraine improvement, and these mechanistic pathways may be parallel and synergistic.

Hindiyeh et al[42] and Ahn[8] have identified mechanisms common to both exercise and migraine including endogenous opioids, endocannabinoids, calcitonin gene-related peptides (CGRP), and brain-derived neurotrophic factor (BDNF). Additional biological pathways potentially linking aerobic exercise to migraine are listed in Table 1. We do not profess to have included all possible candidate mechanisms; rather, we present candidates worthy of consideration and further exploration based on our review of the evidence and our assessment of their potential applicability. For each mechanism or marker listed we cite sample evidence supporting that they are: (1) affected by exercise; and (2) linked to migraine.

The mechanisms and markers in Table 1 can variously be characterized as neuroinflammatory, neurovascular, neurolimbic, neuroendocrine, and/or psychological and behavioral. These processes are known based on the exercise literature to be operational in exercise physiology, and based on the headache literature to be operational in migraine pathophysiology. Any one or more of these mechanisms or markers, operating independently, synergistically, or perhaps antagonistically, may play a role in the link between aerobic exercise and migraine improvement.

Table 1.—Mechanisms and Markers Potentially Linking Aerobic Exercise and Migraine Improvement

Biological (Neuroinflammatory, neurovascular, neurolimbic, neuroendocrine)	Inflammatory[43-47] (IL-6, CRP) Cerebrovascular (vasomotor tone/nitric oxide,[4] vasovagal activity,[48] cerebral blood flow[49-51]) Neuromodulatory[52] (CGRP,[42,53,54] BDNF,[42,55,56] and serotonergic,[57,58] endocannabinoid,[8,42,59,60] and opioidergic[42,61-63] functions) Cortical spreading depression[51,64-66] Information processing[5,67-69] Hormonal (estrogen, progesterone)[70-73]
Psychological and Behavioral	Social-cognitive (self-efficacy,[25,74-80] outcome expectancies,[25,81,82] social support[6]) Locus of control[75,76,80,83,84] Affect and mood state,[85-89] psychological stress,[90-94] catastrophizing? Psychopathology (depression, anxiety)[85,95-98]

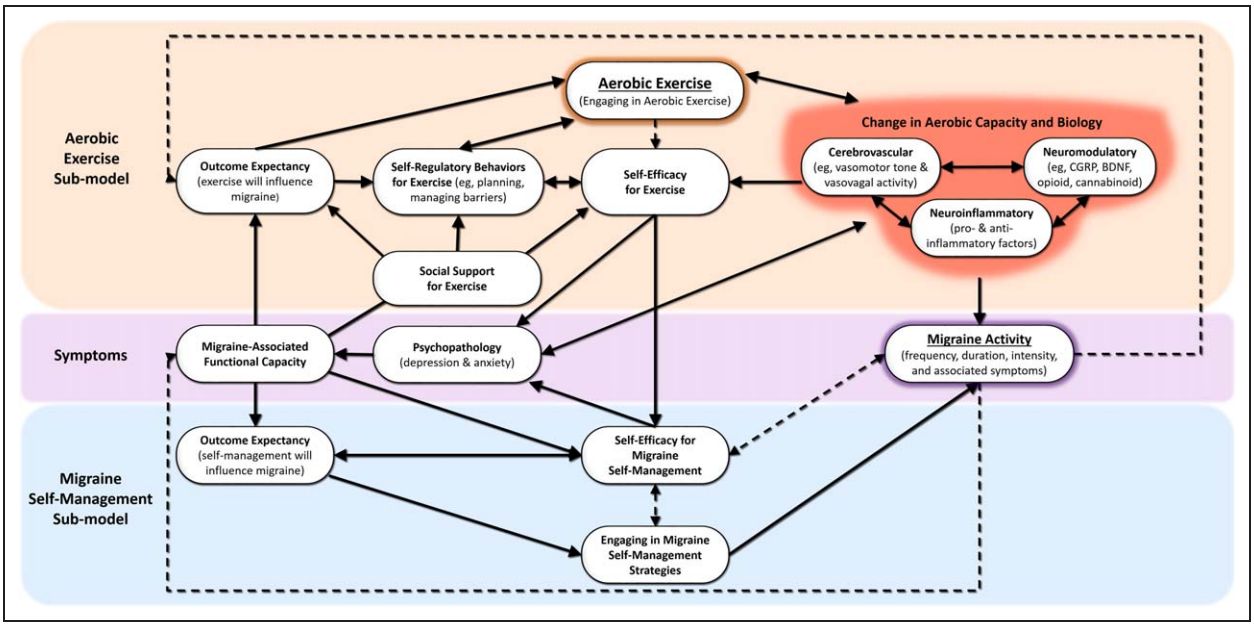

Fig. 1.—Aerobic exercise for reducing migraine burden: a complex model emphasizing social-cognitive factors.

Conceptual Models Articulating the Role of Exercise in Reducing the Burden of Migraine: A Complex Exemplar Model.—Listing these potential mechanisms and markers is, of course, only a starting point. The true value of this process will be realized only once we develop an understanding of how these various factors interrelate – in other words, possess a clearly articulated and ultimately validated conceptual model. Conceivably every item listed in Table 1 could be incorporated into a single working model that could guide future research initiatives and priorities. While valuable, such a model by definition would be highly complex. In Figure 1, we present an exemplar of such a conceptual model and include it principally for purposes of illustration of the types of models that can be built and how the various factors might interact. And although it is considerably complex, it stops short of integrating all factors listed in Table 1.

For this illustration, we have conceptualized the impact of aerobic exercise on migraine activity (the primary endpoint of this model) via two distinct, parallel, and interacting submodels: an *Aerobic Exercise*

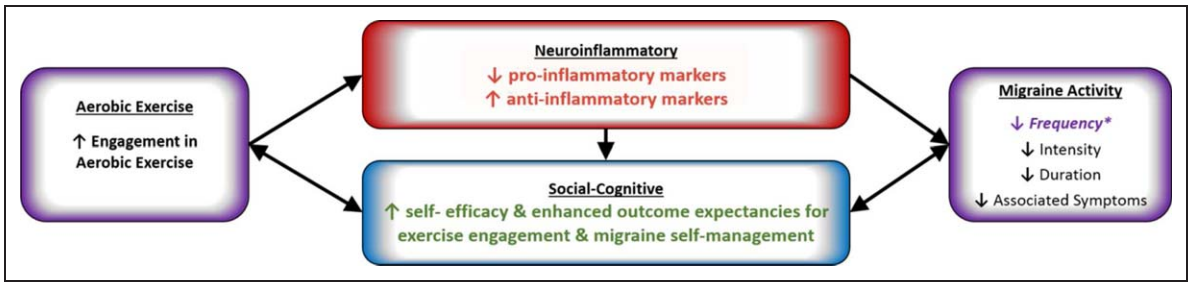

Fig. 2.—Aerobic exercise for reducing migraine burden: a simple model emphasizing social-cognitive factors.

Submodel and a *Migraine Self-Management Submodel* (Fig. 1). The *Aerobic Exercise Sub model* assumes changes in aerobic fitness will influence migraine activity through various physiological and psychological/behavioral pathways. The latter constructs in this sub model are drawn principally from Social-Cognitive Theory as articulated within the exercise literature and pertinent to the engagement in and maintenance of regular aerobic exercise. The constructs in the *Migraine Self-Management Submodel* principally are drawn from Social-Cognitive Theory as well as general models of psychotherapeutic change as articulated in the headache literature. This submodel emphasizes the impact of successful engagement in aerobic exercise on cognitive and behavioral processes thought to mediate or moderate migraine activity.[25,74,75,95,99,100]

While these submodels can be conceptualized independently, we acknowledge and expect that they function in an integrated, synergistic fashion. Nevertheless, we have chosen to articulate the overall model in this way not only to delineate between distinct processes occurring within each pathway, but also to acknowledge that the *Migraine Self-Management Submodel* as described likely operates similarly within any self-management approach to migraine treatment (eg, yoga, relaxation, anaerobic exercise).

Intermediate between the two submodels is a characterization of symptoms including: (1) the endpoint (migraine activity); (2) perceived migraine-associated functional capacity; and (3) psychopathology. Including these constructs as such is intended to acknowledge the role and impact of these symptom constellations as either mediators or moderators within both submodels.

We acknowledge that the social-cognitive/behavioral aspects of this model are considerably better developed than the biological aspects – indeed only just a few of the neurophysiologic mechanisms and markers listed in Table 1 have been incorporated and in minimal detail (shaded in red, Fig. 1). The imbalance in this development is, of course, not a necessary feature of an exercise/migraine model and merely reflects the immediate interests of our team. For example, the model does not include weight loss or sleep as potential mediators.

A Testable, Sample Model Linking Aerobic Exercise and Migraine.—Although useful as a heuristic, the model in Figure 1 does not lend itself to empirical testing. A simplified and disaggregated model, though less complete, might be more testable. In Figure 2, we present a simplified conceptual model that incorporates just a few of the components drawn from the more complex model and includes only two pathways from aerobic exercise to migraine activity.

Such a simplified model might be examined within a single trial. The components of this simplified model are described below and include a *Neuroinflammatory Pathway*, and a parallel *Social-Cognitive Pathway* linking aerobic exercise to changes in migraine activity. Among the many potential mechanisms and markers that could be tested in a model of aerobic exercise and migraine, we chose these two pathways due to their well-established salience to both aerobic exercise and migraine, the ample empirical support for the hypothesized relationships, and the pertinence of these factors to the authors.

Migraine Activity (primary endpoint).—Migraine activity per unit of time was selected as the primary endpoint of this model as a summary target for the benefits of aerobic exercise. We can conceptualize it as a composite measure that reflects the summed area under the pain-associated symptom-disability-time curves.

Engagement in Aerobic Exercise (independent variable).—Whereas physical activity is broadly defined as any bodily movement produced by skeletal muscles that results in energy expenditure, exercise (a subset of physical activity) refers to physical activities that are planned, structured, repetitive, and purposive for the improvement or maintenance of one or more aspects of physical health.[101] Aerobic or cardiovascular exercise refers to any form of bodily movement fueled by aerobic energy-generating processes, where the energy demands of the exercise do not exceed the rate at which the cardiovascular system can supply oxygen to working muscles.[102] Aerobic activity differs from anaerobic activity based on the duration and intensity of muscular contractions and the processes through which energy is generated within muscles to fuel activity. Typically, aerobic exercises include activities performed at sub-maximal intensities that can endure for extended periods of time (eg, walking, jogging, swimming), whereas anaerobic activities (eg, explosive movements, weight lifting, sprinting) rely primarily on rapid breakdown of glycogen in the absence of oxygen. When there is a shortage of oxygen, as in anaerobic activity, glycogen metabolism results in a buildup of lactate that prevents prolonged activity. Aerobic exercise refers to those activities that can be performed at low enough intensities that carbohydrates from glycogen and fat reserves can be aerobically metabolized into energy (oxidation of glucose into pyruvate) over longer periods of time without generating high concentrations of lactate. The US Department of Health and Human Services, the Guidelines from the American College of Sports Medicine, and the American Heart Association recommend all adults accumulate either 150 minutes per week of moderate-intensity aerobic activity or 75 minutes per week of vigorous-intensity aerobic activity (in sustained bouts of at least 10 minutes in duration) for the purpose of promoting and maintaining health benefits.[103,104]

Neuroinflammatory Pathway.—In this model, the inflammatory pathway refers to the balance of anti-inflammatory and proinflammatory processes. Imbalances arise due to abnormalities of systemic anti-inflammatory feedback and hyperactivity of proinflammatory response mechanisms. Abnormalities within the adaptive systems responsible for inflammation regulation may result in failure to effectively resolve inflammation, which contributes to the pathogenesis of various physical and mental health conditions (eg, obesity, depression, cardiovascular disease) including migraine.

Given that inflammatory mechanisms feature prominently in migraine pain, some researchers have hypothesized that migraine is a syndrome of self-limited neurogenic inflammation.[43,44,105,106] Though there are competing arguments to this claim, elevated plasma concentrations of C-reactive protein (CRP), pro-inflammatory cytokines (eg, CGRP, substance P) and alterations in adipocytokines (eg, TNF-α, IL-6), have been implicated in migraine pathogenesis.[107-110] Aberrant systemic inflammation exacerbates the migraine process, and modest improvements in the presence and regulation of systemic and neurogenic inflammation may therefore yield migraine improvement – even in the absence of a chronic, inflammatory disorder.[111-115] Studies consistently show an inverse association between inflammatory markers and physical activity, particularly with long-term engagement in exercise accompanied by weight loss.[45,116] Small scale interventions suggest exercise participation can diminish inflammation, implying that exercise targets inflammatory pathways potentially responsible for reducing pain and disability.[46] Change in inflammation may be more likely to occur with moderate-vigorous physical activity, and regular and chronic exercise not only leads to lowering of systemic inflammatory markers, but reduces inflammatory responses to acute bouts of exercise.[45,47,116,117] In terms of migraine, either or both of these mechanisms may be operating. Given the absence of basal inflammatory elevation in

migraine, we would not expect to find a dramatic reduction in neuroinflammation following exercise intervention. Nevertheless, the fact that exercise can change inflammatory responses in acute exercise suggests that exercise may play a role in migraine activity as much of the neurogenic inflammatory dysregulation characterized in migraine is observed acutely during migraine attacks. As a result of regular engagement in exercise, the anti-inflammatory response of even an acute bout of exercise may offer protection against systemic and neurovascular inflammation.[47]

Social-Cognitive Pathway.—Our model includes two distinct measures of efficacy expectancies (self-efficacy) rooted in Social-Cognitive Theory[40,41,99] and relevant to the impact of aerobic exercise in migraine activity: *Self-Efficacy for Exercise Engagement* (perceived capability and confidence to engage in regular exercise despite the presence of barriers), and *Self-Efficacy for Migraine Self-Management* (perceived capability and confidence to manage migraine). Behavioral migraine therapies repeatedly have been shown to enhance self-efficacy for managing headaches, and, in turn, headache treatment outcomes.[25,75-78] Both forms of self-efficacy are posited to play a role in the symptom improvements achieved with aerobic exercise for migraine. Although conceptualized as separate and distinct from the aerobic and inflammatory pathways, efficacy expectancies are likely to exert an influence that is complimentary or synergistic.

Our model also includes two distinct measures of outcome expectancies[41,81,118,119] likewise rooted in Social-Cognitive Theory that refer to judgments about potential migraine outcomes likely to stem from either engagement in aerobic exercise or in migraine self-management behaviors: *Outcome Expectancies for Exercise Engagement* (one's evaluation of whether participating in regular exercise will result in improvements in migraine activity) and *Outcome Expectancies for Migraine Self-Management* (one's evaluation of whether engaging in migraine self-management strategies will result in improvements in migraine activity). As a rule, assessment of self-efficacy, particularly in relation to pain management, should be accompanied by an assessment of outcome expectancies to best predict future pain management behaviors.[120]

CONCLUSION

Although engagement in regular exercise routinely is recommended as a means of managing and preventing migraine, the empirical support for this recommendation is well less than definitive, and we have at best a weak understanding of the relationship between aerobic exercise and migraine let alone the optimal parameters of exercise regimens for migraine (eg, when to recommend, who will benefit, level of anticipated benefit, optimal types and doses/intensities of exercise). These fundamental knowledge gaps critically limit our capacity to competently deploy exercise as an intervention for migraine. Definitive information is needed regarding the genuine and unique contributions of aerobic exercise for migraine management as well as the capacity for this intervention strategy to be administered as a complement to extant, well-validated pharmacologic and non-pharmacologic migraine therapies.

Assuming the value of aerobic exercise is confirmed for reducing the burden of migraine (we assume it likely will be), then a clear articulation of the mechanisms and pathways through which such benefits are conferred would prove invaluable for informing implementation of exercise therapy for migraine. Moreover, this line of research conceivably will yield new insights on migraine pathophysiology. Once the data are in, we may learn that a number of specific mechanisms and pathways are operational in the relationship between exercise and migraine improvement, and it of course remains to be seen whether these pathways operate in parallel or synergistically. We know fundamentally that regular engagement in aerobic exercise yields fitness enhancements are mediated through changes in a number of cardiopulmonary, inflammatory, and neurovascular processes. Given that migraine is both a neurovascular and a neuroinflammatory disorder, inflammatory, and neurovascular pathways are obvious candidates for study as mechanistic pathways. Beyond neurophysiologic pathways, improvements in aerobic fitness and

migraine likely are mediated by overlapping changes in psychological, behavioral, and sociocognitive factors (eg, self-efficacy beliefs, outcome expectancies) for both exercise participation and migraine self-management.

Hoping to facilitate and encourage research in this arena, we have articulated a variety of potential mechanisms and markers that could account for the effects of aerobic exercise on migraine and are worthy of empirical exploration. It is not our intention to present this as a definitive listing of all possible candidate mechanisms, but we anticipate our readers may share our surprise upon learning just how many factors may be operational – let alone how complex their interrelationships may be. For purposes of illustration, we have included two conceptual models – one quite complex, the other simpler and more pragmatic. Once again, it is not our intention to present these as definitive models but rather as heuristics that not only might demonstrate the potential complexity of these mechanisms but also might benefit conceptually our research programs here forward. Should the promise of aerobic exercise as a feasible and effective migraine therapy be realized, this line of endeavor stands to benefit migraineurs (including the many who presently remain suboptimally treated) by providing a new therapeutic avenue as an alternative or augmentative compliment to established interventions for migraine.

REFERENCES

1. Baillie LE, Gabriele JM, Penzien DB. A systematic review of behavioral headache interventions with an aerobic exercise component. *Headache.* 2014;54:40-53.
2. Busch V, Gaul C. Exercise in migraine therapy-is there any evidence for efficacy? A critical review. *Headache.* 2008;48:890-899.
3. Darabaneanu S, Overath CH, Rubin D, et al. Aerobic exercise as a therapy option for migraine: A pilot study. *Int J Sports Med.* 2011;32:455-460.
4. Narin SO, Pinar L, Erbas D, Oztürk V, Idiman F. The effects of exercise and exercise-related changes in blood nitric oxide level on migraine headache. *Clin Rehabil*. 2003;17:624–630.
5. Overath C, Darabaneanu S, Evers M, et al. Does an aerobic exercise program have an influence on information processing in migraineurs? *J Headache Pain.* 2014;15:1–10.
6. Fitterling JM, Martin JE, Gramling S, Cole P, Milan MA. Behavioral management of exercise training in vascular headache patients: An investigation of exercise adherence and headache activity. *J Appl Behav Anal* 1988;21:9-19.
7. Varkey E, Cider A, Carlsson J, Linde M. Exercise as migraine prophylaxis: A randomized study using relaxation and topiramate as controls. *Cephalalgia.* 2011;31:1428-1438.
8. Ahn AH. Why does increased exercise decrease migraine? *Curr Pain Headache Rep.* 2013;17:379–384.
9. Buse DC, Manack A, Serrano D, Turkel C, Lipton RB. Sociodemographic and comorbidity profiles of chronic migraine and episodic migraine sufferers. *J Neurol Neurosurg Psychiatry.* 2010;81:428-432.
10. Bigal ME, Lipton RB. The epidemiology, burden, and comorbidities of migraine. *Neurol Clin.* 2009; 27:321-334.
11. Scher AI, Bigal ME, Lipton RB. Comorbidity of migraine. *Curr Opin Neurol.* 2005;18:305-310.
12. Wang SJ, Chen PK, Fuh JL. Comorbidities of migraine. *Front Neurol.* 2010;1:1–9.
13. Stathopoulou G, Powers MB, Berry A, Smits J, Otto MW. Exercise interventions for mental health: A quantitative and qualitative review. *Clin Psychol Sci Pract.* 2006;13:179-193.
14. Trivedi MH, Greer TL, Church TS, et al. Exercise as an augmentation treatment for nonremitted major depressive disorder: A randomized, parallel dose comparison. *J Clin Psychiatry.* 2011;72:677-684.
15. Blumenthal JA, Babyak MA, Moore KA, et al. Effects of exercise training on older patients with major depression. *Arch Intern Med*. 1999;159: 2349–2356.
16. Jackson JL, Shimeall W, Sessums L, et al. Tricyclic antidepressants and headaches: Systematic review and meta-analysis. *BMJ.* 2010;341:c5222.
17. Brosse AL, Sheets ES, Lett HS, Blumenthal JA. Exercise and the treatment of clinical depression in adults: Recent findings and future directions. *Sports Med.* 2002;32:741-760.
18. Ernst C, Olson AK, Pinel JPJ, Lam RW, Christie BR. Antidepressant effects of exercise: Evidence

for an adult-neurogenesis hypothesis? *J Psychiatry Neurosci.* 2006;31:84-92.
19. Duman RS. Neurotrophic factors and regulation of mood: Role of exercise, diet and metabolism. *Neurobiol Aging.* 2005;26(Supp1):88-93.
20. Rethorst CD, Toups MS, Greer TL, et al. Pro-inflammatory cytokines as predictors of antidepressant effects of exercise in major depressive disorder. *Mol Psychiatry.* 2013;18:1119-1124.
21. Mattson MP, Maudsley S, Martin B. BDNF and 5-HT: A dynamic duo in age-related neuronal plasticity and neurodegenerative disorders. *Trends Neurosci.* 2004;27:589-594.
22. Leary MR, Downs DL. Interpersonal functions of the self-esteem motive: The self-esteem system as a sociometer. In: Kernis MH, ed. *Efficacy, Agency, and Self-Esteem.* New York: Springer; 1995:123-144.
23. McAuley E, Blissmer B, Katula J, Duncan TE, Mihalko SL. Physical activity, self-esteem, and self-efficacy relationships in older adults: A randomized controlled trial. *Ann Behav Med.* 2000;22:131-139.
24. McAuley E, Mihalko SL, Bane SM. Exercise and self-esteem in middle-aged adults: Multidimensional relationships and physical fitness and self-efficacy influences. *J Behav Med.* 1997;20:67-83.
25. Seng EK, Holroyd KA. Dynamics of changes in self-efficacy and locus of control expectancies in the behavioral and drug treatment of severe migraine. *Ann Behav Med.* 2010;40:235-247.
26. Neusüss K, Neumann B, Steinhoff BJ, Thegeder H, Bauer A, Reimers D. Physical activity and fitness in patients with headache disorders. *Int J Sports Med.* 1997;18:607-611.
27. Stronks DL, Tulen JHM, Bussmann JBJ, Mulder LJMM, Passchier J. Interictal daily functioning in migraine. *Cephalalgia.* 2004;24:271-279.
28. Bond DS, Thomas JG, O'Leary KC, et al. Objectively-measured physical activity in obese women with and without migraine. *Cephalalgia.* 2014;35: 866–893.
29. Hougaard A, Amin F, Hauge AW, Ashina M, Olesen J. Provocation of migraine with aura using natural trigger factors. *Neurology.* 2013;80: 428-431.
30. Varkey E, Cider Å, Carlsson J, Linde M. A Study to evaluate the feasibility of an aerobic exercise program in patients with migraine. *Headache.* 2009;49:563-570.
31. Crombez G, Eccleston C, Van Damme S, Vlaeyen JWS, Karoly P. Fear-avoidance model of chronic pain: The next generation. *Clin J Pain.* 2012;28: 475-483.
32. Martins IP, Gouveia RG, Parreira E. Kinesiophobia in migraine. *J Pain.* 2006;7:445-451.
33. Turk DC, Wilson HD. Fear of pain as a prognostic factor in chronic pain: Conceptual models, assessment, and treatment implications. *Curr Pain Headache Rep.* 2010;14:88-95.
34. (IHS) HCC of the IHS. The International Classification of Headache Disorders, 3rd Edition (beta version). *Cephalalgia.* 2013;33:629-808.
35. Alvarez R, Ramon C, Pascual J. Clues in the differential diagnosis of primary vs. secondary cough, exercise, and sexual headaches. *Headache.* 2014;54:1560-1562.
36. Ramadan NM. Sports-related headache. *Curr Pain Headache Rep.* 2004;8:301-305.
37. Kelman L. The triggers or precipitants of the acute migraine attack. *Cephalalgia.* 2007;27:394-402.
38. Koppen H, van Veldhoven PL. Migraineurs with exercise-triggered attacks have a distinct migraine. *J Headache Pain.* 2013;14:99.
39. Dishman RK, Berthoud H-R, Booth FW, et al. Neurobiology of exercise. *Obesity (Silver Spring).* 2006;14:345-356.
40. Bandura A. Self-efficacy. In: Ramachandran VS, ed. *Encyclopedia of Human Behavior.* Vol 4. New York: Elsevier; 1994;4:71-81.
41. Bandura A. Self-efficacy: Toward a unifying theory of behavioral change. *Psychol Rev.* 1977; 84:191-215.
42. Hindiyeh NA, Krusz JC, Cowan RP. Does exercise make migraines worse and tension type headaches better? *Curr Pain Headache Rep.* 2013;17:380–385.
43. Peroutka SJ. Neurogenic inflammation and migraine: Implications for the therapeutics. *Mol Interv.* 2005;5:304-311.
44. Waeber C, Moskowitz MA. Migraine as an inflammatory disorder. *Neurology.* 2005;52:663-671.
45. Beavers KM, Brinkley TE, Nicklas BJ. Effect of exercise training on chronic inflammation. *Clin Chim Acta.* 2010;411:785-793.
46. Nicklas BJ, Brinkley TE. Exercise training as a treatment for chronic inflammation in the elderly. *Exerc Sport Sci Rev.* 2009;37:165-170.

47. Petersen AMW, Pedersen BK. The anti-inflammatory effect of exercise. *J Appl Physiol.* 2005; 98:1154-1162.
48. Gass JJ, Glaros AG. Autonomic dysregulation in headache patients. *Appl Psychophysiol Biofeedback.* 2013;38:257-263.
49. Ogoh S, Ainslie PN. Cerebral blood flow during exercise: mechanisms of regulation. *J Appl Physiol.* 2009; 107:1370-1380.
50. Ogoh S, Ainslie PN. Regulatory mechanisms of cerebral blood flow during exercise: New concepts. *Exerc Sport Sci Rev.* 2009;37:123-129.
51. Bolay H, Reuter U, Dunn AK, Huang Z, Boas DA, Moskowitz MA. Intrinsic brain activity triggers trigeminal meningeal afferents in a migraine model. *Nat Med.* 2002;8:136-142.
52. Lin T-W, Kuo Y-M. Exercise benefits brain function: The monoamine connection. *Brain Sci.* 2013;3:39-53.
53. Durham PL. Calcitonin gene-related peptide (CGRP) and migraine. *Headache J Head Face Pain.* 2006;46:S3-S8.
54. Bigal ME, Walter S, Rapoport AM. Calcitonin gene-related peptide (CGRP) and migraine current understanding and state of development. *Headache.* 2013;53:1230-1244.
55. Huang T, Larsen KT, Ried-Larsen M, Møller NC, Andersen LB. The effects of physical activity and exercise on brain-derived neurotrophic factor in healthy humans: A review. *Scand J Med Sci Sports.* 2014;24:1-10.
56. Cotman CW, Berchtold NC. Exercise: A behavioral intervention to enhance brain health and plasticity. *Trends Neurosci.* 2002;25:295-301.
57. Silberstein SD. Serotonin (5-HT) and migraine. *Headache.* 1994;34:408-417.
58. Young SN. How to increase serotonin in the human brain without drugs. *J Psychiatry Neurosci.* 2007;32:394-399.
59. Akerman S, Holland PR, Lasalandra MP, Goadsby PJ. Endocannabinoids in the brainstem modulate dural trigeminovascular nociceptive traffic via CB1 and "triptan" receptors: Implications in migraine. *J Neurosci.* 2013;33:14869-14877.
60. Sparling PB, Giuffrida A, Piomelli D, Rosskopf L, Dietrich A. Exercise activates the endocannabinoid system. *Neuroreport.* 2003;14:2209-2211.
61. Boecker H, Sprenger T, Spilker ME, et al. The runner's high: Opioidergic mechanisms in the human brain. *Cereb Cortex.* 2008;18:2523-2531.
62. Genazzani AR, Nappi G, Facchinetti F, et al. Progressive impairment of CSF beta-EP levels in migraine sufferers. *Pain.* 1984;18:127-133.
63. Misra UK, Kalita J, Tripathi GM, Bhoi SK. Is β endorphin related to migraine headache and its relief? *Cephalalgia.* 2013;33:316-322.
64. Monteiro HMC, de Lima e Silva D, de França JPBD, et al. Differential effects of physical exercise and L-arginine on cortical spreading depression in developing rats. *Nutr Neurosci.* 2011;14: 112-118.
65. Levy D. Endogenous mechanisms underlying the activation and sensitization of meningeal nociceptors: The role of immuno-vascular interactions and cortical spreading depression. *Curr Pain Headache Rep.* 2012;16:270-277.
66. Zhang X, Levy D, Noseda R, Kainz V, Jakubowski M, Burstein R. Activation of meningeal nociceptors by cortical spreading depression: Implications for migraine with aura. *J Neurosci.* 2010;30:8807-8814.
67. Kropp P, Gerber WD. Slow cortical potentials in migraine. Predictive value and possible novel therapeutic strategies to prevent an attack. *Funct Neurol.* 2005;20:193-197.
68. Smith PJ, Blumenthal JA, Hoffman BM, et al. Aerobic exercise and neurocognitive performance: A meta-analytic review of randomized controlled trials. *Psychosom Med.* 2010;72:239-252.
69. Colcombe SJ, Kramer AF. Fitness effects on the cognitive function of older adults: A meta-analytic study. *Psychol Sci.* 2003;14:125-130.
70. Bonen A, Ling WY, MacIntyre KP, Neil R, McGrail JC, Belcastro AN. Effects of exercise on the serum concentrations of FSH, LH, progesterone, and estradiol. *Eur J Appl Physiol Occup Physiol.* 1979;42:15-23.
71. Berchtold NC, Kesslak JP, Pike CJ, Adlard PA, Cotman CW. Estrogen and exercise interact to regulate brain-derived neurotrophic factor mRNA and protein expression in the hippocampus. *Eur J Neurosci.* 2001;14:1992-2002.
72. McTiernan A, Tworoger SS, Ulrich CM, et al. Effect of exercise on serum estrogens in postmenopausal women: A 12-month randomized clinical trial. *Cancer Res.* 2004;64:2923-2928.
73. Bentz AT, Schneider CM, Westerlind KC. The relationship between physical activity and 2-hydroxyestrone, 16alpha-hydroxyestrone, and the

2/16 ratio in premenopausal women. *Cancer Causes Control.* 2005;16:455-461.
74. Bandura A, O'Leary A, Taylor CB, Gauthier J, Gossard D. Perceived self-efficacy and pain control: Opioid and nonopioid mechanisms. *J Pers Soc Pyschol*. 1987;53:563–571.
75. French DJ, Holroyd KA, Pinell C, Malinoski PT, O'Donnell F, Hill KR. Perceived self-efficacy and headache-related disability. *Headache.* 2000;40: 647-656.
76. Holroyd KA, Penzien DB, Hursey KG, et al. Change mechanisms in EMG biofeedback training: Cognitive changes underlying improvements in tension headache. *J Consult Clin Psychol.* 1984;52:1039-1053.
77. Bromberg J, Wood ME, Black RA, Surette DA, Zacharoff KL, Chiauzzi EJ. A randomized trial of a web-based intervention to improve migraine self-management and coping. *Headache.* 2012;52: 244-261.
78. Rokicki LA, Holroyd KA, France CR, Lipchik GL, France JL, Kvaal SA. Change mechanisms associated with combined relaxation/EMG biofeedback training for chronic tension headache. *Appl Psychophysiol Biofeedback*. 1997;22:21–41.
79. Holroyd KA, Penzien DB. EMG biofeedback and tension headache: Therapeutic mechanisms. In: Holroyd KA, Schlote BA, Zenz H, eds. *Perspectives in Research on Headache*. Toronto: Hogrefe; 1983:147-162.
80. Martin NJ, Holroyd KA, Rokicki LA. The Headache Self-Efficacy Scale: Adaptation to recurrent headaches. *Headache.* 1993;33:244-248.
81. Spinhoven P, ter Kuile MM. Treatment outcome expectancies and hypnotic susceptibility as moderators of pain reduction in patients with chronic tension-type headache. *Int J Clin Exp Hypn*. 2000;48:290–305.
82. Penzien DB. Neural matrix of pain processing, placebo analgesia, and cognitive factors. *Headache Curr.* 2005;2:139-143.
83. Martin NJ, Holroyd KA, Penzien DB. The headache-specific locus of control scale: Adaptation to recurrent headaches. *Headache J Head Face Pain.* 1990;30:729-734.
84. Scharff L, Turk DC, Marcus DA. The relationship of locus of control and psychosocial-behavioral response in chronic headache. *Headache.* 1995;35: 527-533.
85. Maizels M, Aurora S, Heinricher M. Beyond neurovascular: Migraine as a dysfunctional neurolimbic pain network. *Headache.* 2012;52:1553-1565.
86. Drummond PD, Passchier J. Psychological mechanisms of migraines. In: Olesen J, Goadsby N, Ramadan N, Tfelt-Hansen P, Welch KM, eds. *The Headaches*. 3rd ed. Philadelphia: Lippincott, Williams, & Wilkins; 2006:385-392.
87. Hoffman MD, Hoffman DR. Does aerobic exercise improve pain perception and mood? A review of the evidence related to healthy and chronic pain subjects. *Curr Pain Headache Rep.* 2007;11:93-97.
88. Anderson RJ, Brice S. The mood-enhancing benefits of exercise: Memory biases augment the effect. *Psychol Sport Exerc.* 2011;12:79-82.
89. Scully D, Kremer J, Meade MM, Graham R, Dudgeon K. Physical exercise and psychological well being: A critical review. *Br J Sports Med.* 1998;32:111-120.
90. Sauro KM, Becker WJ. The stress and migraine interaction. *Headache.* 2009;49:1378-1386.
91. Houle TT, Butschek RA, Turner DP, Smitherman TA, Rains JC, Penzien DB. Stress and sleep duration predict headache severity in chronic headache sufferers. *Pain.* 2012;153:2432-2440.
92. Borsook D, Maleki N, Becerra L, McEwen B. Understanding migraine through the lens of maladaptive stress responses: A model disease of allostatic load. *Neuron.* 2012;73:219-234.
93. Holroyd KA, Penzien DB, Rains JC, Lipchik GL, Buse DC. Behavioral management of headache. In: Silberstein SD, Lipton RB, Dalessio DJ, eds. *Wolff's Headache and Other Head Pain*. 8th ed. New York: Oxford University Press; 2008:721-746.
94. Salmon P. Effects of physical exercise on anxiety, depression, and sensitivity to stress. *Clin Psychol Rev.* 2001;21:33-61.
95. Lake AE, Rains JC, Penzien DB, Lipchik GL. Headache and psychiatric comorbidity: Historical context, clinical implications, and research relevance. *Headache.* 2005;45:493-506.
96. Holroyd KA, Labus JS, Carlson B. Moderation and mediation in the psychological and drug treatment of chronic tension-type headache: The role of disorder severity and psychiatric comorbidity. *Pain.* 2009;143:213-222.
97. Smitherman TA, Rains JC, Penzien DB. Psychiatric comorbidities and migraine chronification. *Curr Pain Headache Rep.* 2009;13:326-331.

98. Penzien DB, Smitherman TA, Rains JC. Identifying psychiatric comorbidity in refractory migraine patients. *Refractory Migraine: Mechanisms and Management.* 2010:80-97.
99. Bandura A. *Social Foundations of Thought and Action: A Social Cognitive Theory*. Englewood Cliffs, NJ: Prentice-Hall; 1986.
100. Holroyd KA, Penzien DB, Hursey KG, et al. Change mechanisms in EMG biofeedback training: Cognitive changes underlying improvements in tension headache. *J Consult Clin Psychol.* 1984;52:1039-1053.
101. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Public Health Rep.* 1985;100:126-131.
102. McArdle WD, Katch KI KV. Exercise physiology: Nutrition, energy, and human performance. 7th Edition; 2009:Chapter 21.
103. Pate RR, Pratt M, Blair SN, et al. Physical activity and public health. A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. *JAMA: J Am Med Assoc.* 1995; 273:402-407.
104. Haskell WL, Lee I-M, Pate RR, et al. Physical activity and public health: Updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Circulation.* 2007;116:1081-1093.
105. Moskowitz MA. Neurogenic inflammation in the pathophysiology and treatment of migraine. *Neurology.* 1993;43:S16-S20.
106. Dalessio D. Vascular permeability and vasoactive substances: Their relationship to migraine. *Adv Neurol.* 1974;4:395-401.
107. Peterlin BL, Rapoport AM, Kurth T. Migraine and obesity: Epidemiology, mechanisms, and implications. *Headache.* 2010;50:631-648.
108. Bond DS, Roth J, Nash JM, Wing RR. Migraine and obesity: Epidemiology, possible mechanisms and the potential role of weight loss treatment. *Obes Rev.* 2011;12:e362–371.
109. Rainero I, Pinessi L, Salani G, et al. A polymorphism in the interleukin-1α gene influences the clinical features of migraine. *Headache.* 2002;42: 337-340.
110. Evans R, Williams M, Rapoport AM, Peterlin BL. The association of obesity with episodic and chronic migraine. *Headache.* 2012;52:663-671.
111. Bigal ME, Lipton RB, Holland PR, Goadsby PJ. Obesity, migraine, and chronic migraine: Possible mechanisms of interaction. *Neurology.* 2007;68: 1851-1861.
112. Dimitrova AK, Ungaro RC, Lebwohl B, et al. Prevalence of migraine in patients with celiac disease and inflammatory bowel disease. *Headache.* 2013; 53:344-355.
113. Wilund KR. Is the anti-inflammatory effect of regular exercise responsible for reduced cardiovascular disease? *Clin Sci (Lond).* 2007;112:543-555.
114. Marmura MJ, Silberstein SD. Headaches caused by nasal and paranasal sinus disease. *Neurol Clin.* 2014;32:507-523.
115. Chai N, Scher A, Moghekar A, Bond D, Peterlin BL. Obesity and headache: Part I-a systematic review of the epidemiology of obesity and headache. *Headache.* 2014;54:219-234.
116. Beavers KM, Hsu FC, Isom S, et al. Long-term physical activity and inflammatory biomarkers in older adults. *Med Sci Sports Exerc.* 2010;42:2189-2196.
117. Pedersen BK, Nieman DC. Exercise immunology: Integration and regulation. *Immunol Today.* 1998;19:204-206.
118. Resnick B, Zimmerman SI, Orwig D, Furstenberg AL, Magaziner J. Outcome expectations for exercise scale: Utility and psychometrics. *J Gerontol B Psychol Sci Soc Sci.* 2000;55:S352-S356.
119. Linde K, Witt CM, Streng A, et al. The impact of patient expectations on outcomes in four randomized controlled trials of acupuncture in patients with chronic pain. *Pain.* 2007;128:264-271.
120. Miles CL, Pincus T, Carnes D, Taylor SJC, Underwood M. Measuring pain self-efficacy. *Clin J Pain.* 2011;27:461-470.