5-1-2022

Time-of-Day and Chronotype Dependent Effects of Exercise on Migraine Load in People with Chronic Migraines: A Cross-Over Randomized Clinical Trial

Elias M. Malek

TIME-OF-DAY AND CHRONOTYPE DEPENDENT EFFECTS OF EXERCISE ON MIGRAINE LOAD IN PEOPLE WITH CHRONIC MIGRAINES: A CROSS-OVER RANDOMIZED CLINICAL TRIAL

By

Elias M. Malek

Bachelor of Science – Kinesiology
University of Nevada, Las Vegas
2019

A thesis submitted in partial fulfillment
of the requirements for the

Master of Science – Kinesiology

Department of Kinesiology and Nutrition Sciences
School of Integrated Health Science
The Graduate College

University of Nevada, Las Vegas
May 2022

UNLV | GRADUATE COLLEGE

Thesis Approval

The Graduate College
The University of Nevada, Las Vegas

April 06, 2022

This thesis prepared by

Elias M. Malek

entitled

Time-of-Day and Chronotype Dependent Effects of Exercise on Migraine Load in People with Chronic Migraines: A Cross-Over Randomized Clinical Trial

is approved in partial fulfillment of the requirements for the degree of

Master of Science – Kinesiology
Department of Kinesiology and Nutrition Sciences

Graham McGinnis, Ph.D.
Examination Committee Chair

Kathryn Hausbeck Korgan, Ph.D.
Vice Provost for Graduate Education & Dean of the Graduate College

James Navalta, Ph.D.
Examination Committee Member

Brach Poston, Ph.D.
Examination Committee Member

Jennifer Pharr, Ph.D.
Graduate College Faculty Representative

Abstract

Migraines are the most common cause of chronic pain. Effective, non-pharmacological strategies to reduce migraine load are needed. Exercise is an effective strategy, but it is unclear how exercise timing and temporal preference (chronotype) factors modulate the laudatory effects of exercise. **Purpose**: Determine the effects of; 1) time-of-day of exercise, and 2) exercise synchrony with one's chronotype, on migraine load. **Methods**: Participants were 13 sedentary individuals with 8+ migraines/month (age = 30 ± 11 yrs, 167 ± 6 cm, 86 ± 28 kg). Participants were categorized into morning-/evening-types based on the Morning/Eveningness Questionnaire and instructed to complete 1 month of self-selected exercise in the morning or evening (3 sessions per week of 30-min/session at 60-70% of estimated HRmax) in a randomized cross-over design. Migraine burden was assessed before and after each month of exercise via questionnaires (Headache Impact Test [HIT-6], Migraine Disability Assessment Test [MIDAS]). Exercise timing (morning vs evening) as well as synchrony with chronotype (In-Sync (IS); morning-type exercising in the morning or an evening-type exercising in the evening vs Out-of-Sync (OOS); morning-type exercising in the evening and evening-type exercising in the morning). Data was analyzed using a 2 (morning vs evening or IS vs OOS) x 2 (pre, post) repeated measures ANOVA with significance accepted at $p<0.05$. **Results**: MIDAS scores revealed migraine pain and migraine days were both higher at baseline and post-exercise in the ME condition (Main Effect Time of Day; p=0.01 and p=0.01, respectively), while HIT-6 scores tended to decrease following exercise (Main Effect Exercise; p=0.06). In the analysis of exercise synchrony, we observed a significant interaction effect in HIT-6, migraine days, and MIDAS scores (p=0.02, p=0.051, p=0.006 respectively). Post-hoc dependent t-tests revealed…,

suggesting that only IS exercise improved migraine outcomes. **Conclusion**: Our data suggests that exercise timing has limited impact, but prescribing exercise in-sync with chronotype in people with chronic migraines may be an accessible, non-pharmacological option to decreasing migraine load.

Table of Contents

Abstract iii

List of Figures vi

Introduction 1

Methods 6

Results 11

Discussion 19

Conclusion 25

References 26

Curriculum Vitae 34

List of Figures

Figure 1. Representation of study design 8

Figure 2. Representation of average exercise time and adherence for ME and EE 12

Figure 3. Distribution of time-of-exercise and adherence for IS and OOS exercise 13

Figure 4. Changes in migraine load between ME and EE from pre- to post-. 14

Figure 5. Changes in migraine load between IS and OOS exercise from pre- to post-.....16

Figure 6. Gene expression levels represented as a fold change from baseline for PER2, BMAL1, and VEGF across ME and EE 17

Figure 7. Gene expression levels represented as a fold change from baseline for PER2, BMAL1, and VEGF across IS and OOS exercise 18

Introduction

Chronic pain affects millions of US adults each year, with chronic migraines (CM) being one of the most common forms (*23, 8, 18*). Migraine inflicts a large burden on the individuals afflicted by them, as well as a large financial toll, costing the United States between $560 and $635 million dollars annually (*18*). In a recent study conducted by Wong et. al., individuals with migraines were considerably less productive at work (39.1% productivity loss), which in turn created significant monetary loss for both the company and the individual ($6,176/year lost) (*45*). Migraines, with or without aura, are characterized as a cyclic disorder accompanied by headache-like symptoms, and in some sufferers, photophobia, phonophobia, and transient focal neurological symptoms (11). An individual is classified as a chronic migraineur by the International Headache Society when they experience headaches (migraine-like or tension-type-like) at least 15 days each month for more than 3 months, and of these 15 days, 8 of them have migraine-like features (11). Alongside the many negative effects of migraines, migraineurs are at an increased risk of cardiovascular disease (*32*). The true mechanism behind migraine development has yet to be discovered. However, previous work to determine contributing factors that play a significant role in migraine development established that some vascular molecules alongside calcitonin gene-related peptide (CGRP) may play a role in migraine development. CGRP was linked to the trigeminovascular system in 1982 with implications for migraines (10). CGRP is released by the trigeminovascular system during migraine attacks to act as a vasodilator and maintain cerebral blood flow (9). In a study published in 2022 by Mozafarihashjin et. al., vascular endothelial growth factor (VEGF) was shown to be significantly higher in people with CM when compared to control (28). Continued investigation between the

relationship of VEGF in people with CM is necessary to determine plausible treatment plans to decrease migraine load. There are many successful treatments that have been shown to decrease migraine burden but perhaps the most accessible and cost-effective treatment is exercise.

Exercise has been shown to be an efficacious non-pharmacological intervention to reduce migraine load in people with CM. In a randomized clinical trial done by Kroll et. al, three months of aerobic exercise led to a significant decrease in migraine frequency (21.7%), pain (20.1%), and duration (22.8%), as quantified by a diagnostic headache diary completed by people with CM(*23*). Further research confirms that exercise reduces the number of migraine days (*24*). Beyond reducing migraine burden, exercise has the added benefit of successfully treating comorbidities of migraine such as depression, anxiety, and cardiovascular disease. (*Irby, Sacco*). The current medications available for treatment of chronic migraines induce several central nervous system side-effects such as vertigo, somnolescence, ataxia, and aphasia. The majority of people with CM reported that they are hesitant to take prescription medications because of the impact of adverse side effects, with this effect increasing among more severe chronic migraineurs. This avoidance towards medication is supported by the fact that 79% of sufferers have expressed interest in trying novel treatment strategies that are with lower adverse effects (*Gallagher*). With successful implementation, non-pharmacological interventions may lead to decreased use and reliance on prescription drugs. In fact, Varkey et. al. showed that 71% of people with CM decreased the use of medicine to treat their migraines after six months of exercise (39). While exercise has shown proof of concept efficacy, very little

research has focused on important mediators of exercise prescription such as timing and circadian preference.

The human circadian rhythm is a recurring ~24-hour cycle of physiological processes ranging from behavioral patterns of activity/sleep to metabolic and transcriptional regulation at the cellular level. These cycles are driven by a transcriptional feedback loop known as the circadian clock that resides in essentially every cell in the body (29). There are two main transcription factors that make up our circadian clock; brain and muscle arnt-like 1 (Bmal1) and circadian locomotor output cycles kaput (Clock*)*. Clock and Bmal1 form a transcriptionally active heterodimer, which initiates transcription of different clock-controlled genes (CCGs), including negative regulators of the circadian clock like Per2 (which inhibit *BMAL1* expression). Several physiological and behavioral mechanisms operate in synchrony with an individual's circadian rhythm including regulation of body temperature and blood pressure (29). Circadian rhythms are synchronized to our 24-h days by environmental cues known as "zeitgebers" or "time-givers." There are three primary zeitgebers including light, which is considered the strongest input for central circadian pacemaker in the suprachiasmatic nucleus (SCN), as well as food and exercise, which more strongly dictate peripheral rhythms (43). Recent research indicates that the mechanistic origin of migraines comes from the hypothalamus (6), the same brain region that houses the SCN, suggesting a link between the two (16, 48). In support, migraines have been shown to display circadian rhythmicity, and indicates that attacks peak in the morning and mid-day (1). Furthermore, weekly, monthly, and sometimes even yearly cycles can occur where migraines are more common in the Spring and Fall seasons (14). While migraine has been shown to follow rhythmic occurrence, it may differ based on an individual's circadian or

temporal preference, known as their chronotype (36, 37). Chronotypes are separated into three main groups, morning-types, intermediates, and evening-types and can be determined using the Morning/Eveningness Questionnaire (MEQ) or the Munich Chronotype Questionnaire (MCTQ) (30, 31). Research has shown that the temporal distribution of migraines synchronizes with one's chronotype, where morning-types or evening-types experiencing more migraines in the morning/evening respectively (38). When using exercise as a treatment for migraine, it is necessary to understand the effects that exercise may have on a people with CM's circadian rhythm, and how circadian preferences may influence the response to exercise at different times of day.

The circadian rhythm has previously been shown to modulate the perceptual, physiological, and biochemical response to exercise performed at different times of the day. Work by Wahlberg and Astrand where men were exercised at 3:00 AM and 3:00 PM showed that heart rates during exercise at night were consistently lower than daytime exercise, with three to five beats per minute difference (44). Additionally, Kim et al., found that many inflammatory markers such as IL-6 were increased to a greater extent after exercise in the evening than in the morning (21). The human circadian rhythm modulates many cardiovascular risk markers such as heart rate variability at rest and after exercise, indicating an influence of exercise timing on these cardiovascular risk markers (12). Furthermore, a recent systematic review determined that consistent morning exercise facilitated greater exercise adherence and weight loss when compared to evening exercise in obese patients (33). The results of these studies exhibit a difference in physiological response to exercise depending on the time of day. Additional research also indicates a different time-of-day dependent exercise response

between individuals with different chronotypes, suggesting exercising in synchrony (IS) with one's chronotype maybe be better than out of synchrony (OOS). In a study done by Vitale et al., morning-type athletes competing in evening exercise were more likely to develop fatigue, indicating that exercising OOS with one's chronotype may be deleterious (40-42). This is further supported by a study completed by Thomas et al. that showed that circadian phase shifts that are a result of exercise are dependent on chronotype, not just time-of-day of exercise, with data suggesting that OOS exercise for morning types may be worse than OOS exercise for evening types (36). In a similar study, after a morning HIIT session, evening-types presented higher HRV than morning types, indicating differential responses to exercise when exercising IS or OOS with their chronotype (3, 4). These findings suggest that there is a differential physiological response to exercise at different times-of-day which could be further augmented due to chronotype. However, no studies to date have investigated time-of-day dependent exercise prescription in the context of chronic migraine. Understanding this relationship will introduce a novel advance to exercise as a treatment to reduce migraine burden. As such, the purpose of this study was to determine if morning exercise or evening exercise more potently reduced migraine load. Additionally, we assessed if performing exercise in synchrony (IS) with one's chronotype was more effective than out of synch exercise (OOS).

Methods

Adults aged 18-55 years who self-identified as chronic migraineurs (8+ migraines/month) but were otherwise healthy were recruited for this study. All participants were not recreationally active prior to beginning their participation in the study and were nonsmokers, not pregnant, with no history of cardiac, renal, pulmonary, musculoskeletal, or metabolic disease. This study was approved by the University of Nevada, Las Vegas Institutional Review Board (#1607166), and all participants provided written informed consent. This study was registered as a clinical trial with ClinicalTrials.gov (NCT04553445)

Table 1. Demographic Data

	Age (yrs)	Height (m)	Body Mass (kg)	BMI (kg/m2)
Mean $\pm$ SD	30.1 $\pm$ 11.8	1.67 $\pm$ 0.06	86.95 $\pm$ 28.86	31.1 $\pm$ 9.39

Table 1. Demographic data of the participants included in the present study.

Lab visits –

Participants completed two 1-month exercise interventions in a randomized crossed over design. Laboratory visits took place at the beginning (pre-) and end (post-) of each exercise condition. Participants were provided with instructions for the exercise, as well as a Polar H9 ECG heart rate monitor (Polar Electro, Lake Success, NY) to track and log their exercise sessions throughout the study using the Polar App (a timestamp of each exercise session is provided in

the app, allowing for adherence to timing to be assessed). At each visit, body composition was measured and questionnaires to determine chronotype (MEQ) and migraine load (HIT-6 and MIDAS) were completed. Additionally, a blood sample was collected (~0.6 mL) via finger stick technique, which was used for the assessment of circadian clock gene expression.

Questionnaires –

During the first visit, participants completed the Current Exercise Training Questionnaire to determine current physical activity level (this was used to recruit 'sedentary' participants). At the first, and each subsequent visit, participants completed the Morning/Eveningness Questionnaire (MEQ) to determine their chronotype. The distribution of exercise prescription was assessed in two separate analyses. Firstly, the effects of the time of day of exercise were assessed by comparing Pre and Post values from Morning Exercise (ME) and Evening Exercise (EE). Secondly, the effects of synchrony with chronotype were assessed by separating participant data into IS and OOS groups based on their chronotype *and* exercise timing. IS data was classified as a morning-type exercising in the morning and an evening-type exercising in the evening, while OOS exercise was classified as morning-types exercising in the evening and evening types exercising in the morning.

Migraine load was evaluated using the Headache Impact Test (HIT-6) (34, 46) and Migraine Disability Assessment Test (MIDAS) which are both valid and reliable tools for measuring the impact of chronic migraines (46, 35). MIDAS scores are reported as a value between 0 and 21 with migraine days and migraine pain intensity being recorded during the questionnaire but evaluated separately. For both questionnaires, lower scores indicate lower migraine burden.

Exercise –

Participants completed two months of exercise in a randomized, cross-over design with a two-week wash-out period in between each month of exercise. During each month, participants were instructed to engage in moderate-intensity exercise (60-70% estimated heart rate max, 3 I x per week, 30-min/session, 12 sessions total). Age predicted heart rate max was determined by subtracting their age from 220 (CDC). During the month of Morning Exercise (ME), participants were instructed to complete exercise sessions any time before 9:00 AM. During the month of Evening Exercise (EE), exercise sessions were completed after 7:00 PM. Participants were instructed to complete three workouts per week for four weeks, amounting to twelve total workouts during each month of the study. Time of day of exercise, exercise session

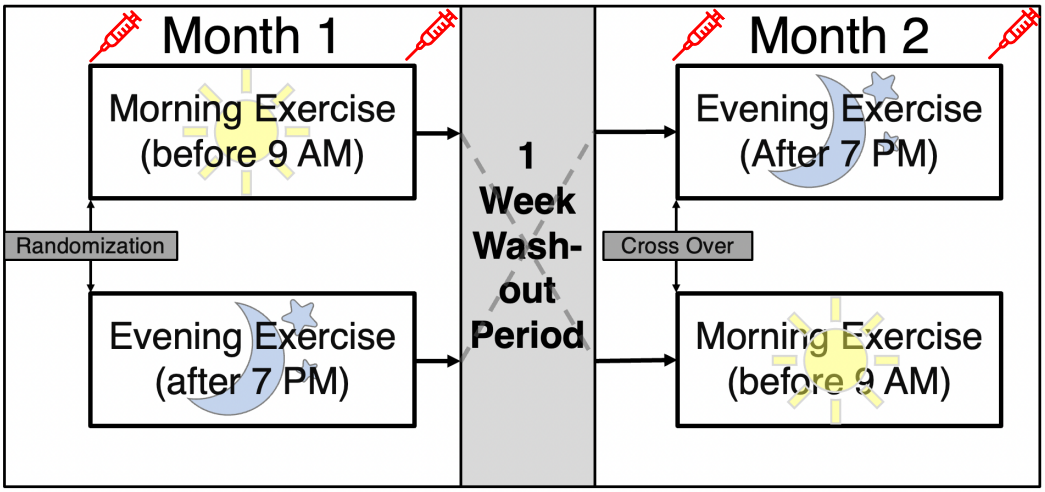

Figure 1. Representation of study design. Questionnaires and blood draws occurred at each syringe marker.

duration, exercise intensity (average heart rate), and adherence to the exercise prescription ([number of sessions completed]/12) were determined from the exercise log (recorded in Polar App). Each variable was compared between ME vs EE, as well as between IS and OOS exercise.

Anthropomorphic data –

Body composition data were collected during each visit. Height was measured using a stadiometer. Total body weight and body fat percentage were measured using bioelectrical impedance (SECA, Chino, CA).

RNA Isolation –

During each visit, capillary blood was drawn using the sterile finger stick technique into an EDTA coated capillary tube and immediately stored on ice. Blood was mixed 1:5 with Erythrocyte lysis buffer (Qiagen, Hilden, Germany), incubated for 15 minutes on ice, and centrifuged to isolate leukocytes for downstream analysis of gene expression. Leukocyte pellets were homogenized with trizol (Life Technologies, Carlsbad, CA) and RNA was isolated using commercially available RNA isolation kits (Qiagen, Hilden, Germany and Zymo, Irvine, CA) following manufacturers' instructions. RNA was stored at -80°C until use for RT-PCR.

RT-PCR –

RNA quantity and quality was assessed via NanoDrop (ThermoFisher, Waltham, MA), and 1000 ng of RNA was reverse transcribed into cDNA using iScript cDNA synthesis kits (BioRad, Hercules, CA). cDNA was diluted to 5 ng/uL in DEPC water. Gene expression was quantified using forward and reverse primers custom designed for *BMAL1, PER2, VEGF,* and *ACTB* (serving as a normalizer). Primers were designed using iDTDNA's PrimerQuest design tool (Integrated DNA Technologies, Coralville, Iowa), checked for stem-loop and/or primer dimers via deltaG

(ΔG > 0), and for non-specific amplification via BLAST (minimal genes that have 100% Query Cover). Primer efficiency validation. Gene expression was measured in duplicate reactions of 25 ng cDNA using conventional SYBR green methodology via RT-PCR through 40 cycles, and calculated using 2^{-ddCt}, reported as fold change from the average of all participants baseline values at the beginning of each month of exercise.

Statistical analysis –

Values are reported as mean ± SEM unless otherwise specified. When comparing the average PRE- to POST- change in outcomes between ME and EE, or IS and OOS, we conducted a paired samples t-test. To assess the effects of the time-of-day of exercise (ME vs EE) and synchrony with chronotype (IS vs OOS) on the ability to reduce migraine load, we performed two, 2 x 2 within-subjects repeated-measures ANOVA. Differences in migraine load across the months of ME and EE were assessed with the ANOVA model with fixed factors in terms of exercise (pre- vs. post-), and time-of-day (ME vs. EE), as well as an interaction. The same analysis was completed when assessing the difference in migraine load across the months of IS and OOS exercise with synchrony and exercise set as fixed factors. If an interaction effect was significant, we performed a paired samples t-test to determine where the significant differences occurred, with significance accepted at $p < 0.05$. Analyses were conducted using SPSS version 28 (IBM, New York, NY) and Microsoft Excel (Microsoft, Seattle, WA). In all cases, $p < 0.05$ was considered statistically significant.

Results

Thirteen participants were recruited for this study. Two participants did not have sufficient RNA isolated from their blood to complete PCR, but their data was included in anthropometric and questionnaire data. ME vs. EE outcomes included data from all thirteen participants except for the gene expression data. Two participants' data were excluded from IS vs. OOS statistical analysis because their MEQs indicated that they were intermediate chronotypes, giving their data no IS or OOS classification. For IS vs. OOS outcomes, data for ten participants data is included in this report. Two participants were excluded from gene expression analysis for synchrony due to insufficient RNA yield from their blood. As such, a total of eight participants were included.

Exercise

Time-of-Day (Morning Exercise vs Evening Exercise) –

Average adherence was 76% through both the morning and evening months combined with no difference between morning and evening exercise (ME = 74% $\pm$ 5% vs. EE = 78% $\pm$ 4%, p=0.35). The median exercise times, as shown in figure 2 for the month of ME and EE was 08:22 AM and 08:08 PM, respectively ($p<0.05$). The average exercise duration of exercise bouts was 33.2 $\pm$ 1.6 mins during the month of morning exercise and 34.1 $\pm$ 4.2 mins during the month of evening exercise, with no difference observed between time-of-day of exercise (p=0.81). Average exercise heart rate showed no significant difference across time of day of exercise (ME = 121 $\pm$ 2 bpm vs. EE = 126 $\pm$ 3 bpm, p=0.09). No significant change in body mass was observed (ME = 0.24 $\pm$ 0.45 Kg vs. EE = 0.57 $\pm$ 0.43 Kg, p=0.6).

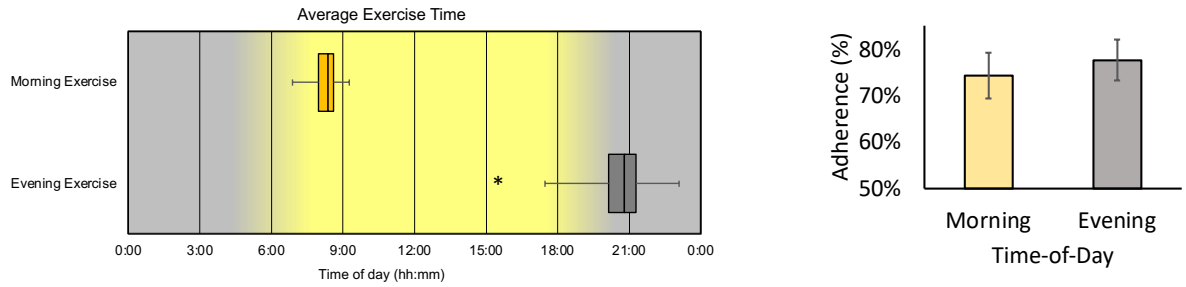

Figure 2. Representation of average exercise time and adherence for ME and EE.

Synchrony –

We observed significantly higher adherence during the month of IS exercise when compared to OOS exercise (IS = 79 $\pm$ 4% vs. 70 $\pm$ 5.5%, p=0.03). Exercise timing during the months of IS and OOS exercise were distributed evenly with the range of exercised times for IS exercise being between 06:52 AM and 11:05 PM and OOS exercise being 07:19 AM and 9:16 PM (p=0.92) (Figure 3). The average exercise duration (IS = 34.8 $\pm$ 5 mins vs OOS = 34.2 $\pm$ 2.6 mins, p=0.88) and average exercise heart rate (IS = 125 $\pm$ 3 bpm vs. EE = 119 $\pm$ 2 bpm, p=0.07) was not significantly different between IS and OOS exercise, although exercise HR showed a near significant trend. There were no significant differences in body mass lost between IS and OOS exercise (IS = 0.54 $\pm$ 0.5 Kg vs. OOS = 0.46 $\pm$ 0.6 Kg, p=0.92).

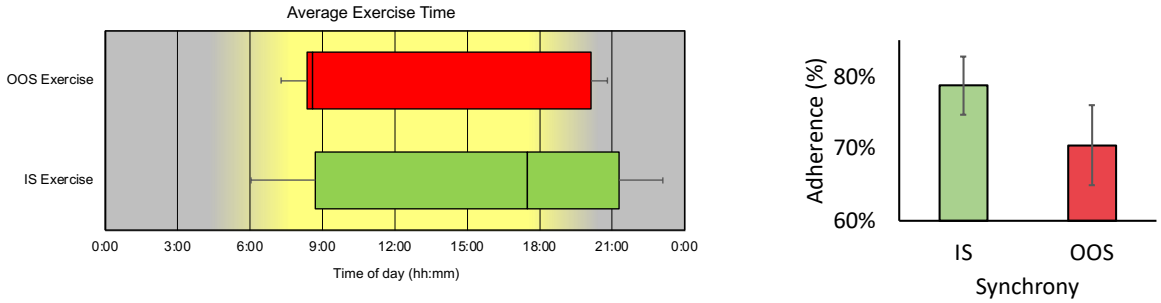

Figure 3. Distribution of time-of-exercise and adherence for IS and OOS exercise.

Migraine Burden

Time-of-Day –

The results of the two-way repeated measures ANOVA are shown in Figure 4. for MIDAS scores revealed a non-significant trend towards a main effect for TOD ($F(1,12)=3.73$, $p=0.07$, $\eta_p^2=0.24$) where MIDAS scores at baseline and after the month of morning exercise were higher during the month of morning exercise (ME = 20.5 ± 4.03 vs. EE = 15.6 ± 3.3, $p=0.07$). The ANOVA results also exhibited no main effect for exercise (pre, post-) ($F(1,12)=0.23$, $p=0.64$, $\eta_p^2=0.02$) and no interaction effect between exercise and TOD ($F(1,12)=2.89$, $p=0.12$, $\eta_p^2=0.194$). The total migraine days showed a significant main effect for TOD ($F(1,12)=8.98$, $p=0.01$, $\eta_p^2=0.43$) such that number of migraine days at both exercises were significantly higher during the month of ME (ME = 12.5 ± 2 days vs. EE = 10.04 ± 2 days, $p=0.01$). Migraine days showed no main effect for exercise ($F(1,12)=0.03$, $p=0.87$, $\eta_p^2=0.002$) and no interaction effect between exercise and TOD ($F(1,12)=1.39$, $p=0.26$, $\eta_p^2=0.104$). Migraine pain did not exhibit a main effect for TOD ($F(1,12)=2.37$, $p=0.15$, $\eta_p^2=0.17$), exercise ($F(1,12)=4.05$, $p=0.07$, $\eta_p^2=0.25$), and no interaction

effect of exercise and TOD ($F(1,12)=0.059$, $p=0.81$, $\eta_p^2=0.005$). HIT-6 scores had no main effect for TOD ($F(1,12)=1.04$, $p=0.33$, $\eta_p^2=0.08$) but there was a near-significant main effect for exercise ($F(1,12)=3.42$, $p=0.09$, $\eta_p^2=0.28$). There was no interaction effect between the two ($F(1,12)=0.56$, $p=0.47$, $\eta_p^2=0.05$).

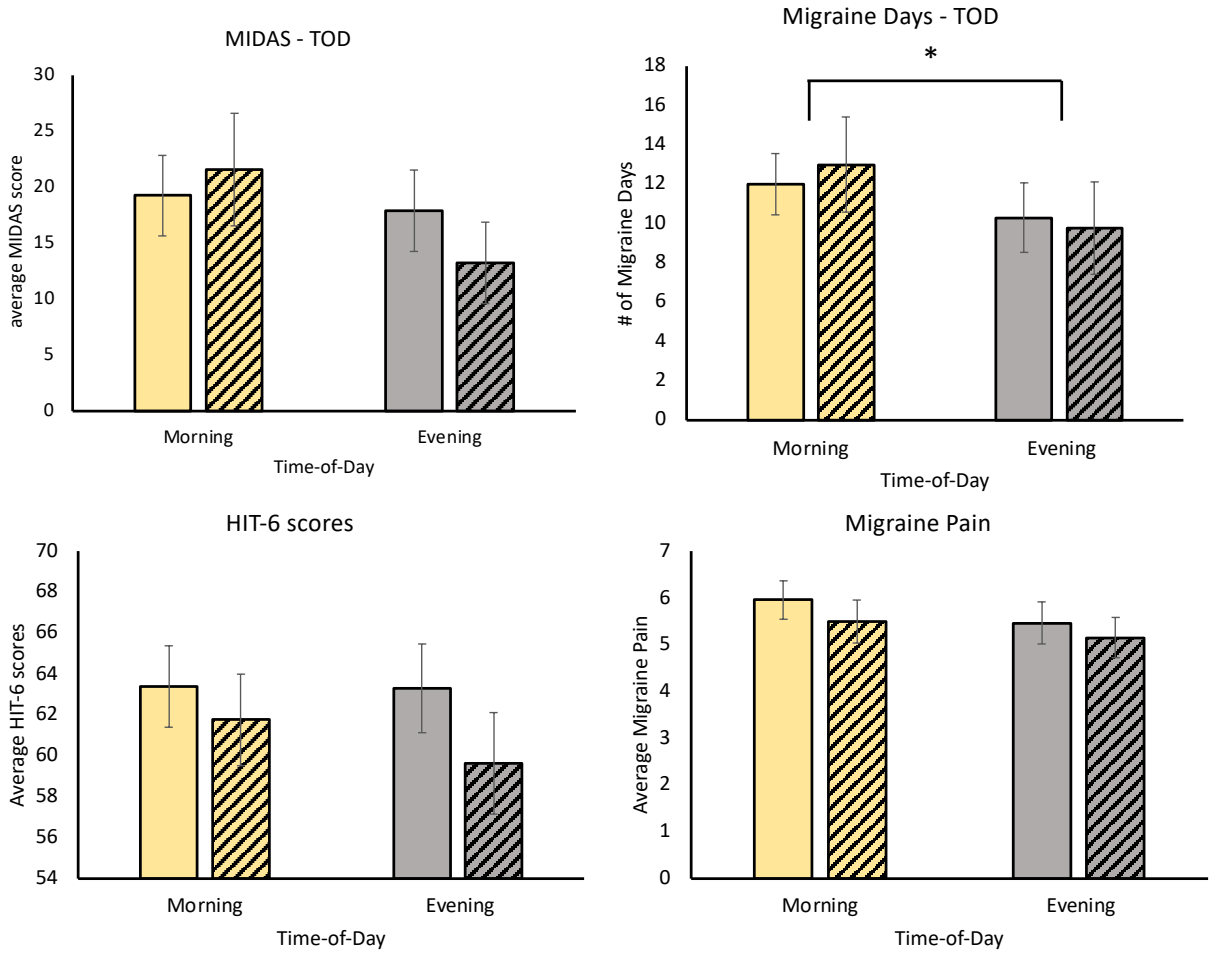

Figure 4. Changes in migraine load between ME and EE from pre- to post-.

Synchrony –

The results of the two-way repeated measures ANOVA are shown in figure 5. MIDAS scores during IS and OOS exercise revealed that there was no main effect of synchrony ($F(1,10) = .002$, $p=0.96$, $\eta_p^2<0.001$) or time ($F(1,10) =1.85$, $p = 0.20$, $\eta_p^2=0.16$). There was a significant interaction effect between time and synchrony for MIDAS scores ($F(1,10)=14.6$, $p = 0.003$, $\eta_p^2=0.59$). Post-hoc tests showed that participant's MIDAS scores improved after IS exercise compared to OOS exercise ($t(10)=3.32$, $p=0.004$, Cohen's $d=1.001$). HIT-6 scores showed a trend towards a main effect of exercise ($F(1,10) =3.84$, $p=0.078$, $\eta_p^2=0.58$) but not for synchrony ($F(1,10) =0.06$, $p=0.82$, $\eta_p^2=0.006$). HIT-6 scores did show a significant synchrony x time interaction effect ($F(1,10) = 8.22$, $p =0.02$, $\eta_p^2=0.45$) where HIT-6 scores improved significantly after IS exercise compared to OOS exercise ($t(10)=2.82$, $p=0.009$, Cohen's $d=0.85$). The number of days that the participants had migraines showed no significant main effect for synchrony ($F(1,10) =.51$, $p=0.49$, $\eta_p^2=0.049$) or exercise ($F(1,10) =2.3$, $p = 0.16$, $\eta_p^2=0.19$) but there was a significant interaction effect between time and synchrony ($F(1,10) =5.76$, $p=0.037$, $\eta_p^2=0.37$) such that number of migraine days decreased after IS exercise but increased after OOS exercise ($t(10)=2.83$, $p=0.009$, Cohen's $d=0.85$). Migraine pain showed no significant main effects for synchrony ($F(1,10) =1.73$, $p=0.22$, $\eta_p^2=0.15$) but there was a near significant main effect of exercise ($F(1,10) =4.93$, $p = 0.051$, $\eta_p^2=0.33$) and no interaction effect as well ($F(1,10) =1.47$, $p=0.25$, $\eta_p^2=0.13$).

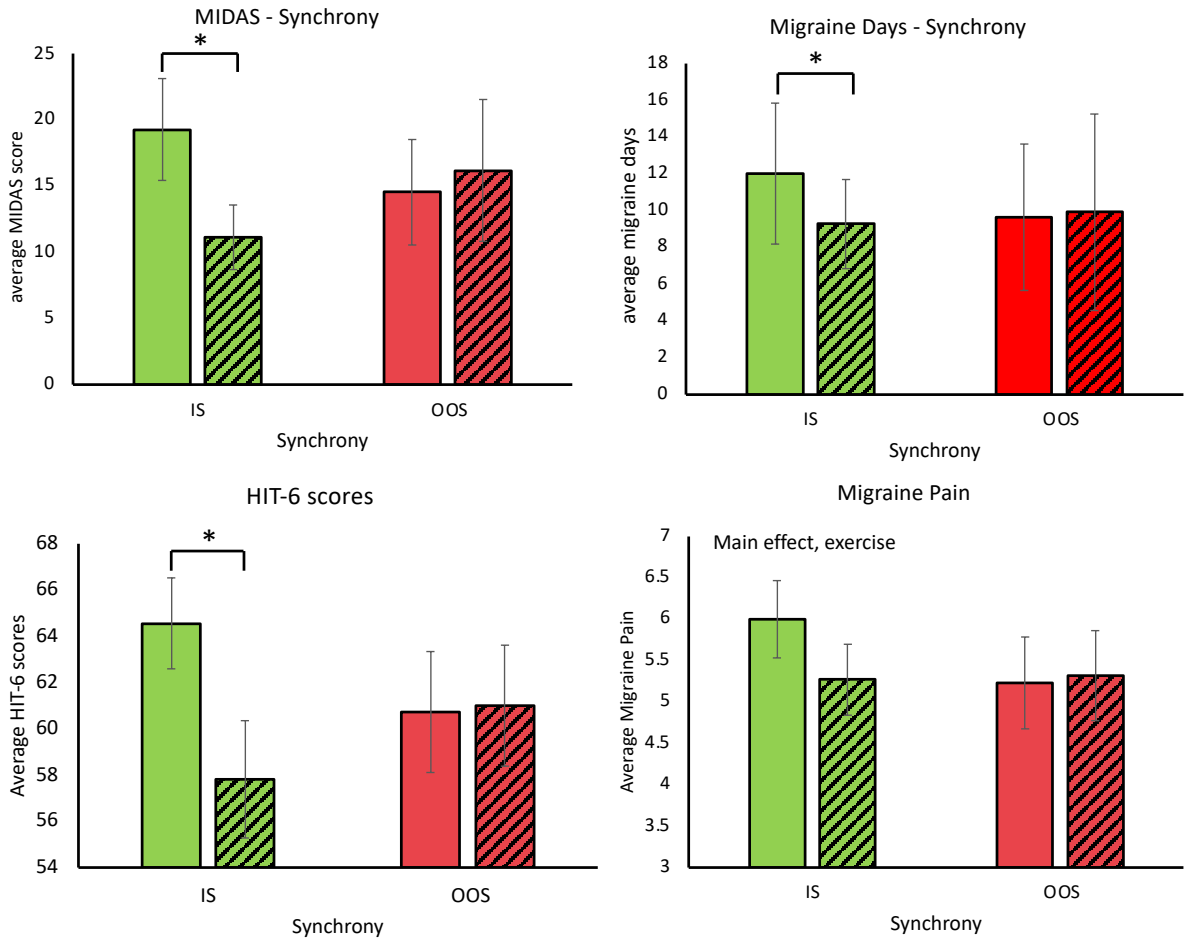

Figure 5. Changes in migraine load between IS and OOS exercise from pre- to post-.

Gene expression

Time-of-day –

Two-way repeated measures ANOVA results indicated that *BMAL1* had no significant main effect of TOD or exercise and no significant interaction effect as well. Analysis of *PER2* showed no main effect of TOD ($F(1,10)=0.102$, $p=0.76$, $\eta_p^2=0.01$) but there was a significant main effect of exercise ($F(1,10)=8.60$, $p=0.02$, $\eta_p^2=0.46$) where *PER2* expression was significantly decreased

after the month of exercise (pre- = 1.00 ± 0.11 vs. post- = 0.71 ± 0.09, p=0.02), independent of TOD. *PER2* analysis showed no interaction effect between exercise and TOD (F(1,10)=0.21, p=0.66, η_p^2=0.02). *VEGF* gene expression data mimicked *PER2* results where there was not main effect of TOD (F(1,10)=1.49, p=0.25, η_p^2=0.13) and the interaction between exercise and TOD (F(1,10)=2.49, p=0.15, η_p^2=0.19). *VEGF* did show a significant main effect for exercise (F(1,10)=7.43, p=0.02, η_p^2=0.43) with *VEGF* decreasing after the month of ME and EE (pre- = 1.00 ± 0.13 vs. post- = 0.82 ± 0.11, p=0.02). These results are exhibited in figure 6.

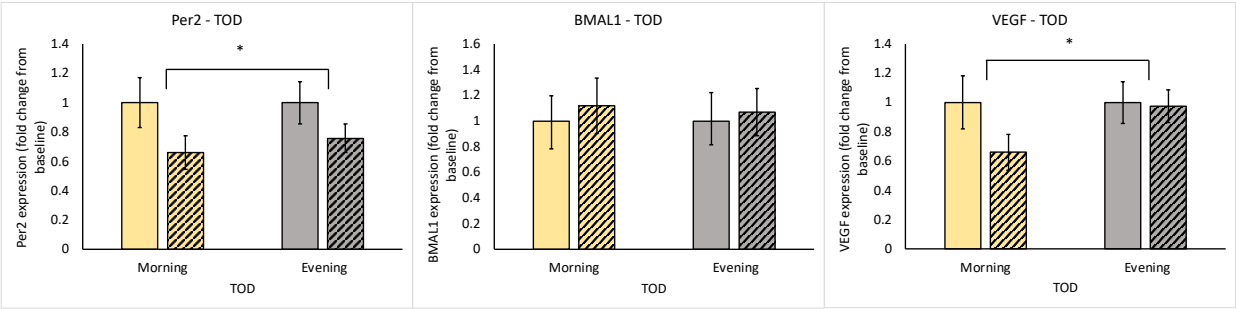

Figure 6. *Gene expression levels represented as a fold change from baseline for PER2, BMAL1, and VEGF across ME and EE.*

Synchrony –

After analysis of PCR data when looking at synchrony, BMAL1 did not exhibit a main effect of synchrony (F(1,9) = 0.32, p=0.58, η_p^2=0.03) or exercise (F(1,9) = 1.22, p=0.29, η_p^2=0.12), or interaction effect between the two (F(1,9)=0.02, p=0.91, η_p^2=0.002). *PER2* analysis did show a significant main effect of synchrony (F(1,8)=5.35, p=0.05, η_p^2=0.401) and exercise (F=(1,8)=8.48, p=0.02, η_p^2=0.52) but no interaction effect between exercise and synchrony (F=(1,8)=1.02,

p=0.34, η_p^2=0.11). *VEGF* expression had no main effect of synchrony (F(1,8)=1.76, p=0.22, η_p^2=0.18) but there was a significant main effect exercise (F(1,8)=6.93, p=0.03, η_p^2=0.46). There was no interaction effect between the two for *VEGF* (F(1,8)=0.14, p=0.72, η_p^2=0.02). All results are shown in figure 7.

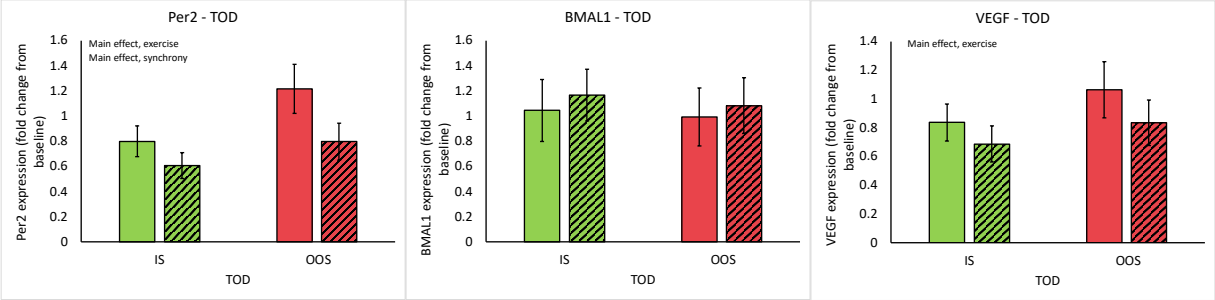

Figure 7. Gene expression levels represented as a fold change from baseline for PER2, BMAL1, and VEGF across IS and OOS exercise.

Discussion

This is the first study to investigate the circadian regulation of exercise induced benefits in people with CM. As far as we know, this is also the first study to show that synchrony with one's chronotype is also an important variable to account for in people with CM using exercise to reduce migraine burden. In a recent systematic review conducted by Vitale et al. in 2017, they found only ten published articles examining the effect of chronotype on exercise performance and perceived exertion. None of the papers reported in this review had participants exercise over a longer period than one day (42). In the current study, we found that migraine outcomes were improved after the month of IS exercise compared to the month of OOS exercise. In particular, MIDAS scores, HIT-6 scores, and migraine days were improved but IS exercise improved HIT-6 scores more than OOS exercise.

Throughout both months of exercise, there was no significant body composition changes, including decreases in body fat percentage or changes in lean mass. Although participants were instructed to complete at least three 30-minute exercise sessions each week, we only had moderate adherence (~75%, not different between conditions). This constitutes a relatively mild exercise intervention that falls below generally recommended exercise prescriptions to see health benefits (ACSM), which could explain why no changes in body composition were observed. We also analyzed the average heart rate and the average minutes per exercise session through the bouts of exercise as a measure of exercise intensity and found no relationship between exercise intensity and migraine burden changes (data not shown). From this information, we can determine that any improvements to migraine load observed in

the current study are independent of any body composition changes or differences in the exercise prescription.

Time-of-Day -

In the current study, we found that migraine days at baseline and after the month of ME were increased when compared to EE. The difference in migraine days across ME and EE months is supported by Alstadhuag et al., where they had patients record their migraines over a twelve-month period and showed that migraines peak in the morning and mid-day (1). Although we did not track *when* migraine attacks occurred, our data does indicate increased migraine load at baseline and after the month of ME when compared to EE. We did not observe a TOD-dependent effect of exercise on improving MIDAS scores, HIT-6 scores, and migraine pain. A systematic review completed by Amin et al., found that in people with CM, regular exercise has been shown to have positive therapeutic outcomes without causing side effects (2). Their findings support our data where, although statistical significance was not reached, HIT-6 scores tended to improve after exercise. This improvement in HIT-6 scores is not influenced by the TOD at which exercise was performed, suggesting that the improvement can be attributed to exercise alone. Varkey et al. designed an aerobic exercise program for untrained chronic migraineurs that was able to increase exercise capacity without making their migraines worse. In many cases, the exercise program actually reduced migraine frequency, intensity, and improved quality of life (39).

We also examined gene expression in the blood after each month of EE and ME. We found that expression of *PER2*, one of the CCGs, was altered in response to exercise where we observed a drop in *PER2* expression after one month of exercise (independent of time of day).

In patients with migraines, a mutation in the circadian gene casein kinase I delta (CKIdelta) causing decreased activity has been identified which may be present among people with CM (5). This decrease in CKI-delta leads to decreased phosphorylation of Per2 (22) as well as a shift in sleep phase (5), which supports our findings where *PER2* was decreased after exercise. In contrast to these findings, Ezagouri et al. conducted a study where mice completed exercise in the morning and in the evening and they found that *PER2* expression was induced after exercise at both time points in skeletal muscle (13). However, these changes were in response to a single exercise bout, not an exercise intervention.

Gene expression analysis revealed a decrease in VEGF expression in response to exercise independent of TOD of exercise. VEGF is one of many regulators of physiological angiogenesis and plasma VEGF is increased in response to exercise in trained and untrained individuals. Alternatively, VEGF has been shown to play a role in the development of migraines. Mozafarihashjin et al. measured peripheral biomarkers in the serum of people with CM and found that VEGF levels were significantly higher in chronic migraine patients when compared to control patients (28). Furthermore, Michalik el al. reported significant decreases in VEGF levels in the interictal period (the time between migraine attacks) compared to control (27). These findings indicate that a reduction in VEGF expression may indicate exercise-induced benefits in our population. While it may be tempting to speculate that the decrease in VEGF expression was the mechanism behind the improvement in migraine load, further investigation into the relationship between exercise timing and VEGF expression in people with CM is necessary for better understanding of their relationship.

Synchrony –

After analyzing the effect of TOD on exercise, we sought to examine the relationship between exercising in-sync or out-of-sync with ones chronotype on exercise adherence, migraine burden, and gene expression. Our data shows that adherence to IS exercise was significantly higher than OOS exercise. To our knowledge, this is the first study to evaluate adherence to an exercise program in this way and represents a clinically impactful tool to improve exercise prescription. These findings suggest that people with CM are more likely to comply with an exercise prescription if the exercise is prescribed IS with that individuals chronotype. Previous studies have shown that people who adhere to exercise are able to manage their migraines in a more capable and confident manner (26, 15). Exercise induced improvements in migraine load subjectively while also decreasing gene expression of vascular genes (*VEGF*) that are involved in migraine development.

In the current study, we also found that IS exercise improves migraine burden outcomes when compared to exercising OOS. MIDAS scores improved after the month of exercise, but scores slightly increased after OOS exercise, with the same pattern being observed in HIT-6 scores. Additionally, the number of migraine days experienced during the month of IS exercise decreased and OOS exercise caused a minor increase. To our knowledge there are no other research studies investigating the effects of exercising IS or OOS following chronic exercise in healthy individuals or people with CM. Data from research studies where individuals completed acute bouts of exercise in the morning and the evening showed that although there was a significant effect of time (ME vs. EE) and a significant effect of chronotype on exercise recovery, there was no interaction between the two variables (41, 42). Sugawara et al. examined the effect of chronotype on post-exercise vagal reactivation and found that evening-types' recovery

following exercise performed at 7:00 AM was worse than morning-types' recovery at the same time (40). These findings align with our hypothesis that exercising IS with one's chronotype will reduce migraine burden when compared to exercising OOS. The results from the present work indicate that when using exercise as an intervention to reduce migraine load in people with CM, it is necessary and important to determine the patient's chronotype and prescribe exercise in-synch with their chronotype to elicit any improvements.

Gene expression analysis between IS and OOS exercise showed that Per2 expression was decreased at baseline and after the month of IS exercise when compared to OOS exercise. PER2 expression was decreased after exercise, independent of synchrony. There may be several explanations for these findings. One possible explanation may be that OOS exercise caused a shift in participant's circadian rhythms because they are exercising OOS of their normal or preferred schedule. Youngstedt et al. has previously shown that exercise causes circadian phase shifts and Thomas et al. determined that exercise exacerbates circadian misalignment depending on the individuals chronotype (47, 36). PER2 is one of many CCGs which would lead to differential expression dependent on circadian phase shifting. VEGF expression was decreased after exercise which follows the same trend as the TOD VEGF expression. These findings support our previous explanation where VEGF is increased among people with CM but exercise decreased VEGF and migraine load improved. Again, the connection between reduced migraine load and decreased VEGF expression is one of many possible explanations.

Limitations –

While our study followed a rather rigorous randomized cross-over design, several limitations exist. First, our participants consisted of 13 chronic migraineurs that were self-

diagnosed (via pre-established cut off criteria for the number of migraine days experienced per month). We may have been able to observe stronger changes if we had followed stricter inclusion criteria where participants had to have a diagnosis from a doctor or were referred from a neurologist. Secondly, while our exercise prescription was designed to be viable to complete alongside work, school, and other responsibilities among our participants, adherence was not perfect. Knowing this, we completed an intent-to-treat analysis rather than excluding participants' data who did not complete the exercise protocol. Our findings still indicate improvements in migraine load, even if adherence was not 100%. Also, while we did control for the TOD of exercise (confirmed by time-stamped exercise logs), and synchrony with chronotype, we did not control for other lifestyle factors such as diet and sleep, which have known impacts on migraine. Our exercise prescription (~90 minutes/week) also falls under ACSM's threshold for cardiovascular exercise to lose weight which is 150 minutes or more of moderate intensity exercise, or 75 minutes of vigorous intensity exercise, per week. Additionally, some participants had trouble with the Polar HR monitors and were unable to record HR for a few exercise sessions, leading to a loss of some adherence and intensity data. Another limitation is that we used two different kits to isolate RNA from leukocytes. We used kits from Zymo and Qiagen. However, we did determine that our PCR results did not differ based on the kit that was used. Lastly, we only collected blood samples at one time of day (which was relatively constant among the entire cohort). This limits our ability to describe the impact of exercise on circadian clock genes, which could be better observed by collecting samples over a 24-hour time-course.

Conclusion

Several papers have identified exercise as an important and valuable intervention to reduce migraine load (23, 24, 20). Further, in healthy individuals, exercise is widely known to have differential physiological responses and adaptations dependent on the time-of-day that it is performed (25). At the time of this study, there is no available literature investigating the efficacy of exercise as an intervention based on the TOD the exercise is performed in people with CM. Additionally, no study on people with CM or healthy individuals subjected to chronic exercise IS or OOS of their chronotype have been performed. Previous research does state that migraine attacks peak in the morning and mid-day (19, 14), which aligns with our findings where migraine load was increased in the morning. Furthermore, IS and OOS exercise was an important variable to consider when assessing the efficacy of the exercise prescription. In particular, migraine burden was not only shown to improve through the month of IS exercise, but OOS had a negative effect on migraine burden. Based on these findings, further research should be conducted to examine the effects of chronotypical synchrony as a critical mediator of the efficacy and adherence to chronic exercise prescriptions in healthy populations as well as other chronic conditions.

References

1. Alstadhaug, K., Salvesen, R., & Bekkelund, S. (2008). *24-Hour Distribution of Migraine Attacks*. *48*(1), 95–100. https://doi.org/10.1111/j.1526-4610.2007.00779.x
2. Amin, F. M., Aristeidou, S., Baraldi, C., Czapinska-Ciepiela, E. K., Ariadni, D. D., Di Lenola, D., Fenech, C., Kampouris, K., Karagiorgis, G., Braschinsky, M., & Linde, M. (2018). *The association between migraine and physical exercise*. *19*(1), 1–9. https://doi.org/10.1186/s10194-018-0902-y
3. Bonato, M., La Torre, A., Saresella, M., Marventano, I., Merati, G., & Vitale, J. A. (2017). *Salivary cortisol concentration after high-intensity interval exercise: Time of day and chronotype effect* (Vol. 34, Issue 6, p. 698). Informa UK Limited. https://doi.org/10.1080/07420528.2017.1311336
4. Bonato, M., ∗, Agnello, L., Galasso, L., Montaruli, A., Roveda, E., Merati, G., Torre, A. L., & Vitale, J. A. (2017). *Acute Modification of Cardiac Autonomic Function of High-Intensity Interval Training in Collegiate Male Soccer Players with Different Chronotype: A Cross- Over Study* (Vol. 16, p. 286).
5. Brennan, K. C., Bates, E. A., Shapiro, R. E., Zyuzin, J., Hallows, W. C., Huang, Y., Lee, H.-Y., Jones, C. R., Fu, Y.-H., Charles, A. C., & Ptáček, L. J. (2013). *Casein kinase iδ mutations in familial migraine and advanced sleep phase*. *5*(183), 183ra56, 1-183ra56. https://doi.org/10.1126/scitranslmed.3005784
6. Burish, M. J., Chen, Z., & Yoo, S. (2019). *Emerging relevance of circadian rhythms in headaches and neuropathic pain*. *225*(1), e13161-n/a. https://doi.org/10.1111/apha.13161

7. Busch, V., & Gaul, C. (2008). *Exercise in Migraine Therapy-Is There Any Evidence for Efficacy? A Critical Review*. *48*(6), 890–899. https://doi.org/10.1111/j.1526-4610.2007.01045.x
8. Degenhardt, L., Erskine, H., Ferrari, A. J., Fitzmaurice, C., Graetz, N., Hansen, G. M., Laurie, E., Liang, X., Ortblad, K., Sandar, L., Abraham, J. P., Abraham, B., Abubakar, I., Abu-Rmeileh, N. M., Achoki, T., Ademi, Z., Alam, S. S., Albittar, M. I., Alemu, Z. A., … Zhang, Y. (2015). *Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013*. *386*(9995), 743–800. https://doi.org/10.1016/S0140-6736(15)60692-4
9. Edvinsson, L. (1985). *Functional role of perivascular peptides in the control of cerebral circulation*. *8*, 126–131. https://doi.org/10.1016/0166-2236(85)90050-5
10. Edvinsson, L., Haanes, K. A., Warfvinge, K., & Krause, D. N. (2018). *CGRP as the target of new migraine therapies — successful translation from bench to clinic*. *14*(6), 338–350. https://doi.org/10.1038/s41582-018-0003-1
11. Ettlin, D. A. (2013). *The International Classification of Headache Disorders, 3rd edition (beta version)*. *33*(9), 629–808. https://doi.org/10.1177/0333102413485658
12. Evoniuk, H., Scheer, F. A. J. L., Shea, S. A., Hu, K., Kelly, E. E., Hilton, M. F., Takahashi, J. S., & Malhotra, A. (2010). *Impact of the human circadian system, exercise, and their interaction on cardiovascular function*. *107*(47), 20541–20546. https://doi.org/10.1073/pnas.1006749107

13. Ezagouri, S., Zwighaft, Z., Sobel, J., Baillieul, S., Doutreleau, S., Ladeuix, B., Golik, M., Verges, S., & Asher, G. (2019). *Physiological and Molecular Dissection of Daily Variance in Exercise Capacity*. *30*(1), 78-91.e4. https://doi.org/10.1016/j.cmet.2019.03.012

14. Fox, A. W., & Davis, R. L. (1998). *Migraine Chronobiology*. *38*(6), 436–441. https://doi.org/10.1046/j.1526-4610.1998.3806436.x

15. French, D. J., Holroyd, K. A., Pinell, C., Malinoski, P. T., O'donnell, F., & Hill, K. R. (2000). *Perceived Self-efficacy and Headache-Related Disability*. *40*(8), 647–656. https://doi.org/10.1046/j.1526-4610.2000.040008647.x

16. Fukuya, H., Emoto, N., Nonaka, H., Yagita, K., Okamura, H., & Yokoyama, M. (2007). *Circadian expression of clock genes in human peripheral leukocytes*. *354*(4), 924–928. https://doi.org/10.1016/j.bbrc.2007.01.063

17. Gallagher, R. M., & Kunkel, R. (2003). *Migraine Medication Attributes Important for Patient Compliance: Concerns About Side Effects May Delay Treatment*. *43*(1), 36–43. https://doi.org/10.1046/j.1526-4610.2003.03006.x

18. Gaskin, D. J., & Richard, P. (2012). *The Economic Costs of Pain in the United States*. *13*(8), 715–724. https://doi.org/10.1016/j.jpain.2012.03.009

19. Gori, S., Morelli, N., Maestri, M., Fabbrini, M., Bonanni, E., & Murri, L. (2005). *Sleep quality, chronotypes and preferential timing of attacks in migraine without aura*. *6*(4), 258–260. https://doi.org/10.1007/s10194-005-0201-2

20. Irby, M. B., Bond, D. S., Lipton, R. B., Nicklas, B., Houle, T. T., & Penzien, D. B. (2016). *Aerobic Exercise for Reducing Migraine Burden: Mechanisms, Markers, and Models of Change Processes*. *56*(2), 357–369. https://doi.org/10.1111/head.12738

21. Kim, H.-K., Konishi, M., Takahashi, M., Tabata, H., Endo, N., Numao, S., Lee, S.-K., Kim, Y.-H., Suzuki, K., & Sakamoto, S. (2015). *Effects of Acute Endurance Exercise Performed in the Morning and Evening on Inflammatory Cytokine and Metabolic Hormone Responses*. *10*(9), e0137567. https://doi.org/10.1371/journal.pone.0137567

22. Knippschild, U., Gocht, A., Wolff, S., Huber, N., Löhler, J., & Stöter, M. (2005). *The casein kinase 1 family: participation in multiple cellular processes in eukaryotes*. *17*(6), 675–689. https://doi.org/10.1016/j.cellsig.2004.12.011

23. Krøll, L. S., Hammarlund, C. S., Linde, M., Gard, G., & Jensen, R. H. (2018). *The effects of aerobic exercise for persons with migraine and co-existing tension-type headache and neck pain. A randomized, controlled, clinical trial*. *38*(12), 1805–1816. https://doi.org/10.1177/0333102417752119

24. Lemmens, J., de Pauw, J., van Soom, T., Michiels, S., Versijpt, J., van Breda, E., Castien, R., & de Hertogh, W. (2019). *The effect of aerobic exercise on the number of migraine days, duration and pain intensity in migraine: A systematic literature review and meta-analysis*. *20*(1), 16. https://doi.org/10.1186/s10194-019-0961-8

25. Lewis, P., Korf, H. W., Kuffer, L., Groß, J. V., & Erren, T. C. (2018). *Exercise time cues (zeitgebers) for human circadian systems can foster health and improve performance: a systematic review*. *4*(1), e000443. https://doi.org/10.1136/bmjsem-2018-000443

26. Linde, M., Jonsson, P., & Hedenrud, T. (2008). *Influence of disease features on adherence to prophylactic migraine medication*. *118*(6), 367–372. https://doi.org/10.1111/j.1600-0404.2008.01042.x

27. Michalak, S., Kalinowska-Lyszczarz, A., Wegrzyn, D., Thielemann, A., Osztynowicz, K., & Kozubski, W. (2017). *The Levels of Circulating Proangiogenic Factors in Migraineurs*. *19*(4), 510–517. https://doi.org/10.1007/s12017-017-8465-7

28. Mozafarihashjin, M., Togha, M., Ghorbani, Z., Farbod, A., Rafiee, P., & Martami, F. (2022). *Assessment of peripheral biomarkers potentially involved in episodic and chronic migraine: a case-control study with a focus on NGF, BDNF, VEGF, and PGE2*. *23*(1), 3. https://doi.org/10.1186/s10194-021-01377-6

29. Panda, S. (2016). *Circadian physiology of metabolism*. *354*(6315), 1008–1015. https://doi.org/10.1126/science.aah4967

30. ROENNEBERG, T. (2012). *What is chronotype? 10*(2), 75–76. https://doi.org/10.1111/j.1479-8425.2012.00541.x

31. Roenneberg, T., Kuehnle, T., Juda, M., Kantermann, T., Allebrandt, K., Gordijn, M., & Merrow, M. (2007). *Epidemiology of the human circadian clock*. *11*(6), 429–438. https://doi.org/10.1016/j.smrv.2007.07.005

32. Sacco, S., Ricci, S., & Carolei, A. (2012). *Migraine and vascular diseases: A review of the evidence and potential implications for management* (Vol. 32, Issue 10, pp. 785–795). SAGE Publications. https://doi.org/10.1177/0333102412451361

33. Schumacher, L. M., Thomas, J. G., Raynor, H. A., Rhodes, R. E., & Bond, D. S. (2020). *Consistent Morning Exercise May Be Beneficial for Individuals With Obesity*. *48*(4), 201–208. https://doi.org/10.1249/JES.0000000000000226

34. Smelt, A. F., Assendelft, W. J. J., Terwee, C. B., Ferrari, M. D., & Blom, J. W. (2014). *What is a clinically relevant change on the HIT-6 questionnaire? An estimation in a primary-*

care population of migraine patients. *34*(1), 29–36. https://doi.org/10.1177/0333102413497599

35. STEWART, W. F., LIPTON, R. B., WHYTE, J., DOWSON, A., KOLODNER, K., LIBERMAN, J. N., & SAWYER, J. (1999). *An international study to assess reliability of the Migraine Disability Assessment (MIDAS) score*. *53*(5), 988–994. https://doi.org/10.1212/WNL.53.5.988
36. Thomas, J. M., Kern, P. A., Bush, H. M., Mcquerry, K. J., Black, W. S., Clasey, J. L., & Pendergast, J. S. (2020). *Circadian rhythm phase shifts caused by timed exercise vary with chronotype* (Vol. 5, Issue 3). American Society for Clinical Investigation. https://doi.org/10.1172/jci.insight.134270
37. van Oosterhout, WPJ, van Someren, E., Schoonman, G. G., Louter, M. A., Lammers, G. J., Ferrari, M. D., & Terwindt, G. M. (2018). *Chronotypes and circadian timing in migraine*. *38*(4), 617–625. https://doi.org/10.1177/0333102417698953
38. van Oosterhout, Wpj, Van Someren, E., Schoonman, G., Louter, M. A., Lammers, G. J., Ferrari, M. D., & Terwindt, G. M. (2018). *Chronotypes and circadian timing in migraine*. *38*(4), 617–625. https://doi.org/10.1177/0333102417698953
39. Varkey, E., Cider, Å., Carlsson, J., & Linde, M. (2009). *A Study to Evaluate the Feasibility of an Aerobic Exercise Program in Patients With Migraine*. *49*(4), 563–570. https://doi.org/10.1111/j.1526-4610.2008.01231.x
40. Vitale, Jacopo A, Bonato, M., Galasso, L., La Torre, A., Merati, G., Montaruli, A., Roveda, E., & Carandente, F. (2017). *Sleep quality and high intensity interval training at two different times of day: A crossover study on the influence of the chronotype in male*

collegiate soccer players (Vol. 34, Issue 2, p. 260). Informa UK Limited. https://doi.org/10.1080/07420528.2016.1256301

41. Vitale, Jacopo Antonino, Bonato, M., La Torre, A. L., & Banfi, G. (2019). *Heart Rate Variability in Sport Performance: Do Time of Day and Chronotype Play A Role?* (Vol. 8, Issue 5). MDPI AG. https://doi.org/10.3390/jcm8050723
42. Vitale, Jacopo Antonino, & Weydahl, A. (2017). *Chronotype, Physical Activity, and Sport Performance: A Systematic Review*. *47*(9), 1859–1868. https://doi.org/10.1007/s40279-017-0741-z
43. Viticchi, G., Falsetti, L., Paolucci, M., Altamura, C., Buratti, L., Salvemini, S., Brunelli, N., Bartolini, M., Vernieri, F., & Silvestrini, M. (2019). *Influence of chronotype on migraine characteristics*. *40*(9), 1841–1848. https://doi.org/10.1007/s10072-019-03886-4
44. Wahlberg, I., & Åstrand, I. (1973). *Physical work capacity during the day and at night*. *10*(2), 65–68. https://www.jstor.org/stable/44376351
45. Wong, L. P., Alias, H., Bhoo-Pathy, N., Chung, I., Chong, Y. C., Kalra, S., & Shah, Z. U. B. S. (2020). *Impact of migraine on workplace productivity and monetary loss: a study of employees in banking sector in Malaysia*. *21*(1), 68. https://doi.org/10.1186/s10194-020-01144-z
46. Yang, M., Rendas-Baum, R., Varon, S. F., & Kosinski, M. (2011). *Validation of the Headache Impact Test (HIT-6^{TM}) across episodic and chronic migraine*. *31*(3), 357–367. https://doi.org/10.1177/0333102410379890
47. Youngstedt, S. D., Elliott, J. A., & Kripke, D. F. (2019). *Human circadian phase–response curves for exercise*. *597*(8), 2253–2268. https://doi.org/10.1113/JP276943

48. Zurak, N. (1997). *Role of the Suprachiasmatic Nucleus in the Pathogenesis of Migraine Attacks*. *17*(7), 723–728. https://doi.org/10.1046/j.1468-2982.1997.1707723.x

Curriculum Vitae

Elias Malek
elias.malek@unlv.edu or eliasmalek24@gmail.com

EDUCATION

M.S., **Kinesiology, University of Nevada, Las Vegas, In-Progress (May 2022 Graduation)**
Thesis: "TIME-OF-DAY AND CHRONOTYPE DEPENDENT EFFECTS OF EXERCISE ON MIGRAINE LOAD IN MIGRAINEURS: A CROSS-OVER RANDOMIZED CLINICAL TRIAL"
Committee: Dr. Graham R. McGinnis, Dr. James Navalta, Dr. Brach Poston, Dr. Jennifer Pharr

B.S., Kinesiology, University of Nevada, Las Vegas, 2020

HONORS AND AWARDS

Graduate Access Grant, UNLV, Fall 2020
Given to graduate students at the discretion of the department

Rebel Achievement Scholarship, UNLV, Fall 2015 – Spring 2020

Millennium Scholarship, UNLV, Fall 2015 – Spring 2020

UNLV Grant, UNLV, Fall 2015 – Spring 2020

Dean's Honor Roll, UNLV, Spring 2018

GPSA Travel Grant, UNLV, Fall 2021

GPSA Research Grant, UNLV, Spring 2022

TEACHING EXPERIENCE

Part Time Instructor, UNLV, Summer 2020
- Exercise physiology lab
- Assisted with exercise physiology lecture

Graduate Teaching Assistant, UNLV, Fall 2020 - Present
- Exercise physiology lab

Undergraduate Teaching Assistant, UNLV, Fall 2018

- Reviewed and edited Psychology 210 course
- Graded exams and assignments throughout the semester

PUBLICATIONS AND PRESENTATIONS

Effect of Exercise in Sync with Circadian Preference on Migraine Load in Migraineurs
ELIAS M. MALEK**,** JAMES W. NAVALTA, FACSM, GRAHAM R. MCGINNIS

Effect of Exercise in Sync with Circadian Preference on Classification of Response and Non-response in Migraineurs
JAMES W. NAVALTA, FACSM, GRAHAM R. MCGINNIS, & **ELIAS M. MALEK** Accepted Abstract at Southwest ACSM

Validity of Average Heart Rate and Energy Expenditure in Polar Armband Devices While Self-Paced Biking
WYATT B. FULLMER, BRYSON CARRIER, DAMIAN GIL, KYLE CRUZ, CHARLI AGUILAR, DUSTIN DAVIS, **ELIAS MALEK**, NATHANIEL BODELL, JEFF MONTES, JAKE MANNING, MARK DEBELISO, FACSM, JAMES W. NAVALTA, FACSM, MARCUS M. LAWRENCE
Accepted Abstract at Southwest ACSM

Validity of Average Heart Rate and Energy Expenditure in Polar OH1 and Verity Sense While Self-Paced Running
DAMIAN GIL, BRYSON CARRIER, WYATT B. FULLMER, KYLE CRUZ, CHARLI AGUILAR, DUSTIN W. DAVIS, **ELIAS MALEK**, NATHANIEL BODELL, JEFF MONTES, JAKE MANNING, JAMES W. NAVALTA, FACSM, MARCUS M. LAWRENCE, MARK DEBELISO, FACSM
Accepted Abstract at Southwest ACSM

Evaluating the Validity of the Salatto-Love and Care of Nature Direct Indication Scale Against the Love and Care of Nature Scale During Rest and After Self-Paced Hiking
RW. SALATTO, DUSTIN W. DAVIS, **ELIAS MALEK**, JAMES W. NAVALTA, FACSM, JEFF MONTES, NATHANIEL BODELL, BYRSON CARRIER, JACOB W. MANNING, & MARK DEBELISO, FACSM
Accepted Abstract at Southwest ACSM

Validity of Average Heart Rate and Energy Expenditure in Polar OH1 and Verity Sense While Self-Paced Walking

NATHANIEL BODELL, BRYSON CARRIER, DAMIAN GIL3, WYATT B. FULLMER, KYLE CRUZ, CHARLI AGUILAR, DUSTIN W. DAVIS, **ELIAS MALEK**, JEFF MONTES, JACOB MANNING, FACSM, JAMES W. NAVALTA, FACSM, MARCUS M. LAWRENCE, MARK DEBELISO
Accepted Abstract at Southwest ACSM

Diurnal Regulation Of Exercise-induced Anabolic And Catabolic Signaling In White Adipose Tissue
Elias Malek, Caitlin Reynolds, Charli Aguilar, MS, Graham McGinnis, PhD
Medicine & Science in Sports and Exercise Poster

Time of Day Dependent Effect on Exercise-induced Autophagy in Striated Mouse Muscle.
Elias Malek, Caitlin Reynolds, Charli Aguilar, MS, Graham McGinnis, PhD
Medicine & Science in Sports and Exercise Poster
UNLV Undergraduate Research Symposium Fall 2019 Presentation/Poster

Diurnal Regulation of Exercise-induced Interleukin-6 Signaling
Charli Aguilar, MS, **Elias Malek**, Caitlin Reynolds, Graham McGinnis, PhD
Medicine & Science in Sports and Exercise Poster

Acute Beta-Alanine Supplementation and Pain Perception Before and After Hiking
James W. Navalta, FACSM, Graham R. McGinnis, Jacob W. Manning, Robert W. Salatto, Bryson Carrier, Dustin W. Davis, Jacquelyn V.L. Sertic, Peyton C. Cater, Brenna Barrios, **Elias M. Malek**, Caitlyn Reynolds, Mark DeBeliso, FACSM
Medicine & Science in Sports and Exercise Poster

Forewarned: Emotional awareness predicts fibromyalgia pain.
Dietz, A. K., Dannen, S., **Malek, E**., Huang, Y., Barchard, K. A., Doherty, H., Williams, D., & Lumley, M. (2019, April).
Poster presented at the Western Psychological Association, Pasadena, CA.

PROFESSIONAL SERVICE

Internship, Total Sports Medicine and Orthopaedic, 2014-2015
Dr. Roddy McGee and Dr. Joseph Yu

- Shadowed Dr. Yu and Dr. McGee
- Did the primary examination for the doctor
- Helped the nurses set up for procedures such as draining of fluids, PRP treatments, injections, etc...

PROFESSIONAL AFFILIATIONS

American College of Sports Medicine
Western Psychological Association
International Journal of Exercise Science

LANGUAGES

English: Native Language
Arabic: Fluent

COMPUTER SKILLS

- Microsoft Office
- ImageJ
- SPSS
- Python
- NanoDrop software

LAB SKILLS

- Western Blotting (extensive experience)
- Protein isolation
- RNA isolation (extensive experience)
- RT-PCR
- Animal Handling
- Metabolic cart testing
- Wearable tech validation
- SPSS statistics
- Animal tissue harvesting
- Scientific writing
- Statistics analyzing
- Creating and optimizing protocols