

Aerobic exercise training for migraine prevention: A trigger-based analysis

Treinamento físico aeróbico na prevenção da migrânea: Uma análise de fatores desencadeantes

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ABSTRACT

Background: Although aerobic exercise has been recommended for migraine management, no study has yet explored the effects of regular aerobic exercise on migraine triggers profile. **Objective:** To evaluate the effects of a 12-week aerobic exercise intervention on migraine triggers profile. **Methods:** We conducted a secondary, post hoc analysis of a randomized, controlled clinical trial. Triggers were recorded in a paper-based headache diary with a formal list including 8 common migraine triggers. Results: Twenty-five patients concluded the protocol and were analysed (exercise: n = 12; waitlist: n = 13). In the whole cohort, the most common triggers were stress/irritability (60 %), sleep deprivation (60 %), fasting (28 %), and foods (28 %). Most patients (52 %) had ≥ 3 triggers. The exercise group showed a higher baseline proportion of patients with ≥ 3 triggers (69 %) compared to waitlist group (25 %) ($p = 0.041$). After intervention period, there was no difference in the proportion of patients with ≥ 3 triggers between waitlist (16.6 %) and exercise (30 %) groups ($p = 0.502$). The exercise group showed greater numeric reductions (from group's sum) than waitlist group for triggers stress/irritability (-14 vs -9), fatigue (-12 vs -6), and menstruation (-9 vs -5). This seemed to reflect the reduced number of attacks in the exercise group [mean (CI95 %): -2.5 (-3.7, -1), $p = 0.002$] vs waitlist [0.9 (2.4, -0.8), $p = 0.341$]. **Conclusion:** Tracking migraine triggers during exercise interventions may help to unravel specific clinical effects of regular exercise. Trial registration: #NCT01972607.

Keywords: Physical Activity, Exercise, Stress, Treatment, Triggers.

RESUMO

Embora o exercício aeróbico seja recomendado no tratamento da migrânea, nenhum estudo seu efeito no padrão de fatores desencadeantes das crises, os chamados “gatilhos”. O objetivo desse estudo foi avaliar se um programa de exercícios aeróbicos de 12 semanas afeta o perfil de gatilhos reportados pelos pacientes. Foi realizada uma análise secundária post hoc de um estudo controlado e randomizado. Os gatilhos foram registrados em diário da dor impresso contendo uma lista de 8 gatilhos frequentemente reportados na literatura. Vinte e cinco participantes concluíram o protocolo e foram analisados. Na amostra total, os gatilhos mais comuns foram estresse/irritabilidade (60 %), privação do sono (60 %), jejum (28 %) e alimentos (28 %). A maioria dos pacientes (52 %) reportaram ≥ 3 gatilhos. O grupo exercício mostrou maior proporção de pacientes com ≥ 3 gatilhos (69 %) no período pré intervenção em comparação com o grupo controle (25 %) ($p = 0.041$). Após intervenção, essa diferença não foi observada (exercício = 30 % vs controle = 16.6, $p = 0.502$). O grupo exercício mostrou maior redução numérica (dados de soma dos gatilhos por grupo) em comparação com o grupo controle para os gatilhos estresse/irritabilidade (-14 vs -9), fadiga (-12 vs -6) e menstruação (-9 vs -5). Esse efeito refletiu redução no número dos ataques no grupo exercício [média (IC 95 %): -2.5 (-3.7, -1), $p = 0.002$] vs grupo controle [0.9 (2.4, -0.8), $p = 0.341$]. O registro no padrão de gatilhos durante intervenções com exercícios pode auxiliar no rastreio de efeitos clínicos específicos ainda não estudados. Registro do estudo clínico: NCT01972607.

Descritores: Atividade Física, Exercício Físico, Migrânea, Fatores Desencadeantes, Estresse.

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INTRODUCTION

Growing body of evidence has strengthened the therapeutic benefits of regular physical activity for the management of migraine¹. In particular, aerobic exercise performed at moderate intensity and practiced 3 times per week is accounted for reducing around 30-40 % the number of migraine attacks/days with migraine²⁻⁴), with therapeutic effects comparable to preventive medication^{5,6}. Other health outcomes such as perceived stress, mood, and well-being may also improve by adopting aerobic exercise as an adjunct treatment for migraine^{2,7,8}. However, there are still other unexplored effects of aerobic exercise on clinical aspects of migraine, such as the triggers profile of patients.

Many patients perceive a myriad of internal or external stimuli as precipitants of migraine attacks, the so-called triggers⁹⁻¹³. A recent meta-analysis showed that nearly 90% of headache patients report at least one consistent trigger⁹. The most common triggers reported by patients include stress, sleep deprivation, fasting, certain foods, menstruation, to name a few⁹. While physical exercise is also considered a trigger by around 20-40 % of patients^{14,15}, many evidences from clinical and epidemiological studies strengthen the recommendation of regular aerobic exercise, and the current understanding is that the protective effect outweighs possible harmful triggered during exercise¹⁶. In fact, exercise imposes a challenge to homeostasis at molecular and physiological levels in several neurobehavioral and physiological processes, it could interact with mechanisms thought to be involved in migraine triggers, such as sleep, stress response, hydration, hypoglycaemia, and so forth to either worse/precipitate the attacks or prevent them¹⁷.

In this sense, exploring the patient's trigger pattern while engaging in an exercise training program may have clinical and behavioural implications, and even affect exercise prescription recommendation for this population. Therefore, it is necessary to understand better the relationship between aerobic exercise and migraine under the perspective of triggers factors. To our knowledge, no study has yet evaluated the response of regular aerobic exercise on the triggers' profile of migraine patients. Thus, the scope of this study was to evaluate the trigger profile of a migraine patient cohort following a 12-week aerobic exercise program. Because there is inter-person variability for triggers, we did not set any a priori hypothesis. We rather conducted an exploratory data analysis, then provided contextual interpretation based on current literature.

METHODS

Study Design

This study consists of a secondary, post hoc, per-protocol analysis of an open-label, randomized controlled clinical trial aiming to assess clinical outcomes in migraine patients following a 12-week aerobic exercise program².

We retrospectively analysed the triggers recorded in the headache diary of patients.

The study protocol was approved by the Research Ethics Committee of the Sao Paulo Federal University, and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All participants gave their informed consent prior to their inclusion in the study. The trial has been registered in the National Institute of Health (www.ClinicalTrials.gov) under #NCT01972607. The study complies with the CONSORT's Statement on data reporting for non-pharmacological trials¹⁸.

Participants

Participants were recruited and screened in the Neurology Department of the Sao Paulo Federal University. The inclusion criteria were: subjects of both sexes, between 18 and 65 years, physically inactive the previous 12 months (defined as ≤ 1 day/week of leisure-time physical activity). Exclusion criteria were: patients taking any prescribed medication or dietary supplements; practicing mind-body activities (e.g., yoga, tai chi, etc.); pregnancy; clinical history of cardiovascular, pulmonary, metabolic, rheumatic, musculoskeletal, psychiatric, or other neurological disease. All participants had a neurological and cardiological examination before inclusion in study.

Migraine Triggers Assessment

Clinical data were retrieved from paper-based headache diary. Besides the data on migraine frequency, the diary had a formal list including eight common migraine triggers: "stress/irritability", "sleep deprivation", "oversleep", "fasting", "foods", "odours", "photoc stimuli", "alcohol", and "other" for non-listed factors. If there were no identifiable triggers, patients were instructed to let the option for description blank.

Statistical Analyses

Descriptive statistics and comparison between groups for participants' characteristics were calculated by independent t-test (normal distribution assumed). Within-group differences for migraine frequency (continuous variable) pre-post intervention were computed by paired t-test. These data are shown as mean and 95 % confidence interval. For triggers/clinical variables analyses, the pre- and post-intervention periods were set as the 4 weeks prior the 12-week intervention period and the last 4 weeks of this intervention period, respectively.

Descriptive statistics for trigger profile are expressed as either group or whole cohort percentage, or group's sum. Comparisons in the proportion of triggers/patient pre and post intervention were calculated by two-sided Exact Fisher's test. Data were computed in the SPSS software (IBM, Version 19.0, Chicago, IL). A *p* value < 0.05 was considered statistically significant.

RESULTS

Twenty-five participants were per-protocol analysed. Table 1 shows participants clinical and anthropometrical characteristics. In the whole cohort, 92 % of patients (23 out of 25 patients) reported at least one trigger during the intervention period. The most common triggers were stress/irritability (15/25 patients, or 60%), sleep deprivation (15/25 patients, or 60%), fasting (7/25 patients, or 28 %), food (7/25 patients, or 28 %), and odours (5/25 patients, or 20%). The groups' trigger profile are shown in the Figure 1. Most patients (13/25, or 52%) ascribed ≥ 3 triggers to their attacks in the baseline period.

Table 1. Participants' characteristics. Data expressed as mean \pm 3 standard deviation, or group' percentage.

Variables	Waitlist	Exercise
Age (years)	34.2 \pm 9.0	37.4 \pm 13.8
Body Mass (kg)	69.6 \pm 18.9	72.9 \pm 15.7
Height (m)	1.63 \pm 0.1	1.64 \pm 0.05
BMI (kg/m ²)	25.9 \pm 6.03	27.0 \pm 4.5
Sex:		
Male, n(%)	3(25)	2(15.4)
Female, n(%)	9(75)	11(84.6)
Time living with migraine (yrs.)	15.6 \pm 8.5	18.2 \pm 13.3
Days w/ Migraine (n/month)	7.6 \pm 4	8.9 \pm 3.6
Attacks Frequency (n/month)	5.1 \pm 2.5	6.3 \pm 3

The exercise group showed a higher baseline proportion of patients with ≥ 3 triggers (69 %) compared to waitlist group (25 %) ($p = 0.041$) (Figure 2). After intervention period, the exercise group showed reduced migraine attack frequency compared to waitlist group [mean (CI 95 %): exercise = -2.5 (-3.7, -1), $p = 0.002$ vs waitlist = 0.9 (2.4, -0.8), $p = 0.341$], while there was no difference in the proportion of patients with ≥ 3 triggers between waitlist (16.6 %) and exercise (30 %) groups ($p = 0.502$) (Figure 2). The exercise group showed greater numeric reductions (i.e., "Δ" values computed from group's sum) than waitlist group for the triggers stress/irritability (-14 vs -9), fatigue (-12 vs -6), and menstruation (-9 vs -5) (Figure 3).

Figure 4 illustrates the flow of migraine triggers for each group across time from baseline to post intervention period. Triggers that were not reported by patients in any period of intervention were designated "no trigger".

DISCUSSION

To our knowledge, this is the first study to evaluate the triggers profile of migraine patients following exercise training. In this secondary analysis, we tracked back the triggers' profile of a migraine patient cohort enrolled in a randomized control trial testing the efficacy of aerobic exercise training for migraine prevention. We intended to identify possible changes in the pattern of trigger profile following the aerobic exercise training protocol.

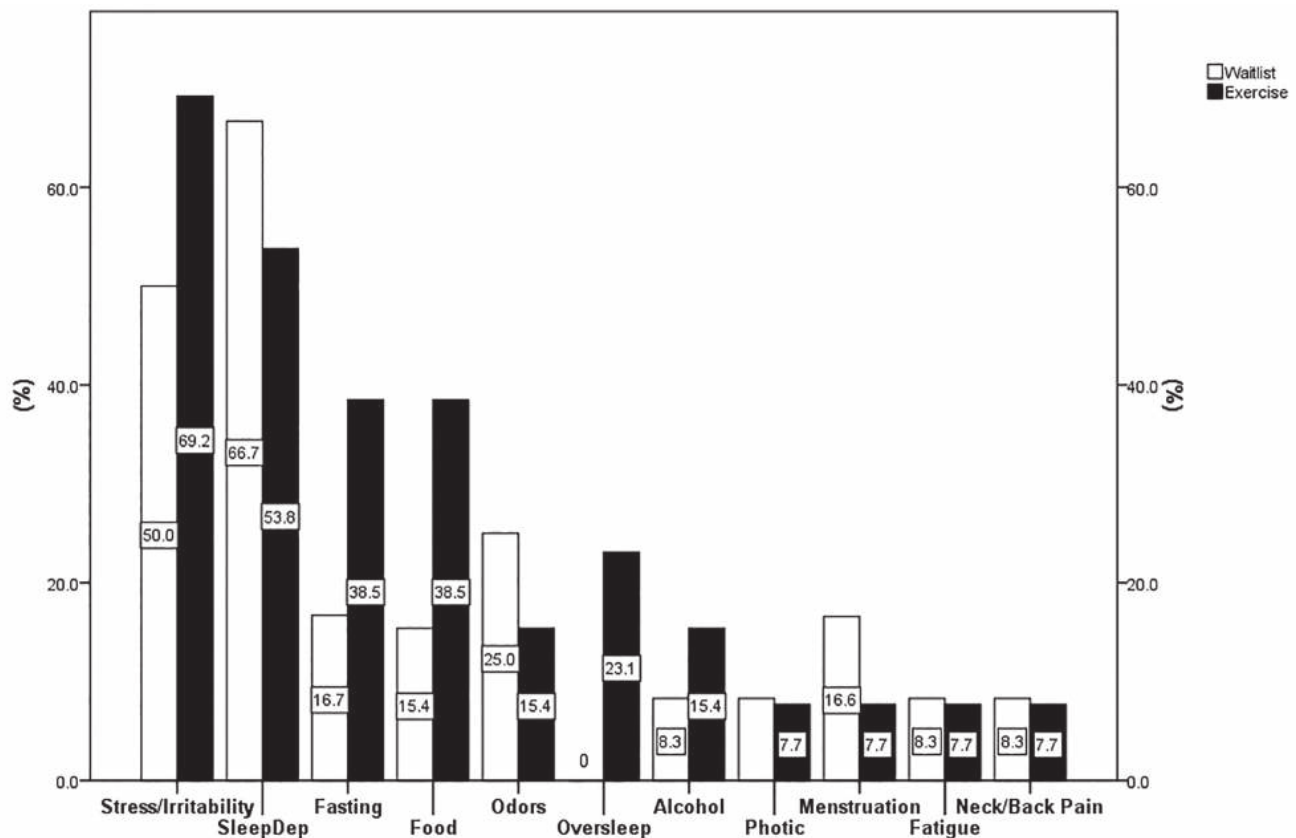


Figure 1. Trigger profile observed in waitlist and exercise groups.

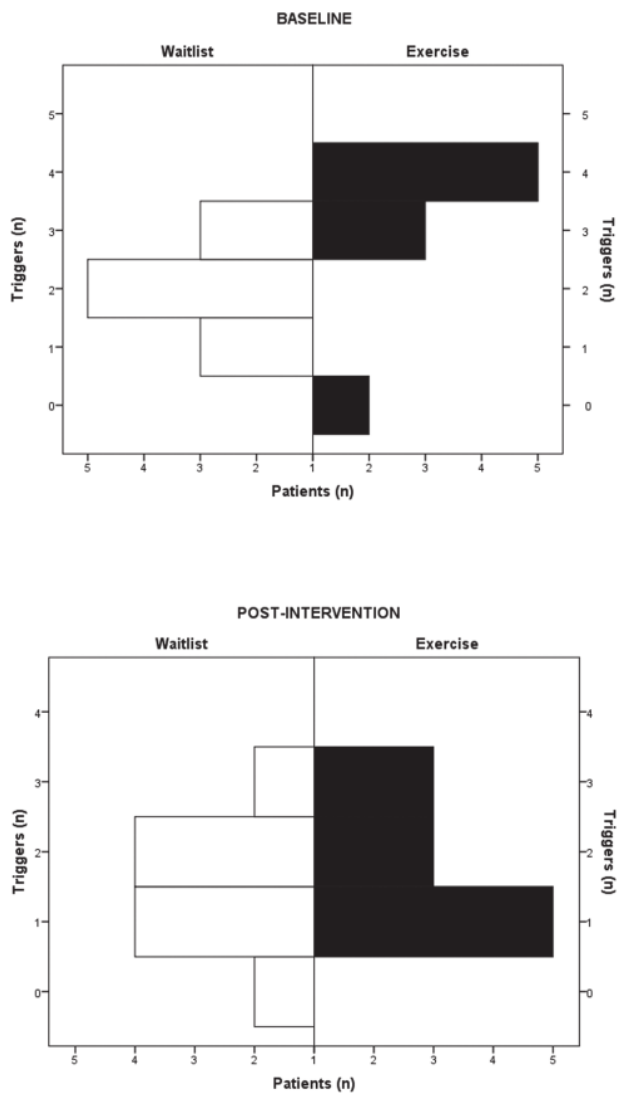


Figure 2. Trigger profile before and after exercise.

We confirmed previous studies showing a high percentage of patients reporting at least one trigger (over 90 %)⁹, as well as we replicated the data showing perceive stress, sleep deprivation, and fasting (skipping meals) as the most common triggers⁹-¹³. We found that the higher proportion of patients with ≥ 3 triggers in the exercise group compared to waitlist group at baseline equalized the waitlist group after intervention period (Figure 2), probably reflecting the reduction in the number of migraine attacks across time with exercise training. This also seemed to be the case regarding the greater numeric reduction for most triggers in the exercise group (Figure 3). Moreover, this larger numeric reduction for some triggers in the exercise group could be due to a greater sample size in this group.

While regular aerobic exercise may reduce migraine frequency¹,³, between 1/4 and 1/3 of migraine patients report physical exercise as a consistent trigger¹⁴,¹⁵. Surprisingly, there was no reported physical exercise-triggered attack in this study. Some explanations to this finding may be the fact that all participants were willing to participate in an exercise program, the exercise intensity was gradually increased up to the level prescribed (moderate intensity around 70% of the age-predicted maximum heart rate) based on cardiorespiratory parameters, and all exercise sessions were supervised.

It is relevant to understand the relation of triggers with physical exercise, since there is no specific exercise prescription recommendation for migraine patients with regard to their personal trigger profile, or whether or not the surge of new popular exercise modalities could be deleterious for the migraine patient. For example, new popular exercise modalities that rapidly gain adepts worldwide such as high intensity interval training¹⁹ or training in a fasted state²⁰, can be challenging for a migraine patient and is impractical to be recommended. On the other hand, in face of positive metabolic and cardiovascular benefit of these exercise modalities, one could question whether a progressive introduction of such exercise types would benefit clinical aspects of migraine, including the trigger pattern. Such trigger

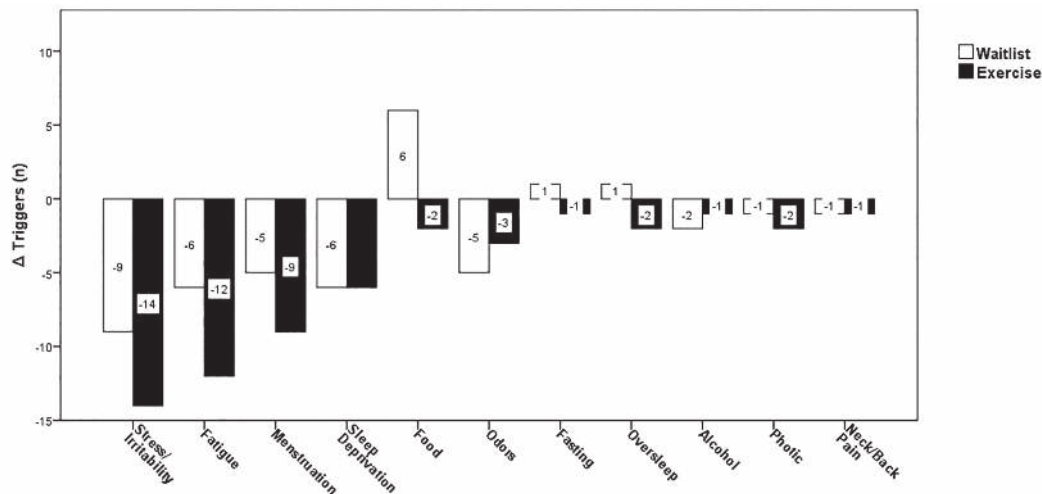


Figure 3. Change in common migraine triggers after intervention period.

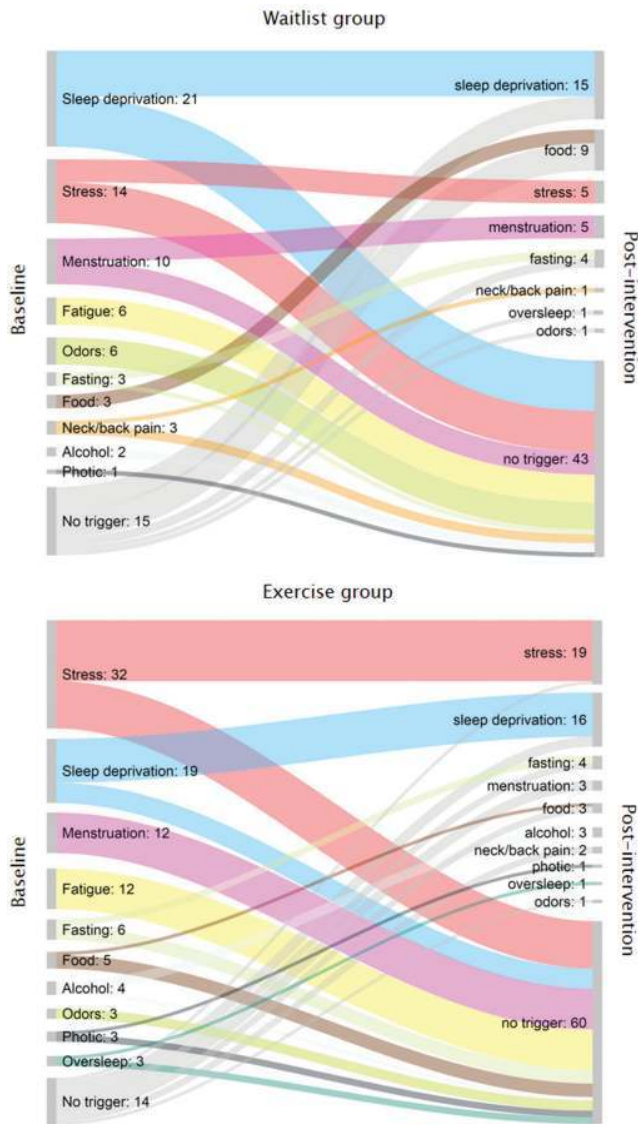


Figure 4. Flow of migraine triggers for each group across time from baseline to post intervention period.

analysis, in clinical practice, could help patients to detect either positive or potentially harmful effects of regular physical activity interacting with subjective triggers. In the future, further studies could establish specific exercise prescription recommendations for this population.

Although the data here do not allow us to draw conclusion for specific effects of exercise training on the pattern of migraine triggers, regular aerobic exercise training mediates several neuroendocrine, neuroimmune, and neuromodulatory processes, which could be accounted for the greater reduction in triggers such as stress/irritability, sleep deprivation, menstruation, neck pain, and fatigue in the intervention group. For example, regular exercise is thought to promote anti-inflammatory

effects²¹, regulate the hypothalamic-pituitary-adrenal axis mediating habituation of stress response²²⁻²⁴, which are akin with the recent evidence of exercise-mediate anxiolysis and lower pro-inflammatory cytokines in migraine women⁷. Also, aerobic exercise may improve sleep quality, and therefore could prevent sleep deprivation-triggered attacks, by changing melatonin production^{25,26}, which in its turn represent an endogenous molecule thought to play a role in the pathomechanisms of migraine disorders²⁷. A recent study showed that aerobic exercise helped to reduce neck pain in a particular subpopulation of patients presenting with both migraine and tension-type headaches²⁸. Less attacks due to fatigue could reflect improvement in oxidative energy metabolism following exercise training through changes in mitochondrial function, which has been also linked to migraine pathophysiology^{29,30}.

There was a large difference in non-identifiable triggers between groups (20 attacks). It is likely that interference from attention and care delivered by researchers to the exercise group during the exercise sessions may have rendered participants more aware of their triggers by speaking with researchers about their personal clinical features.

Limitations and Strengths

There are limitations in this study, which hamper one to generalise our findings. The study is comprised of a small sample of patients interested in adopting aerobic exercise training as a non-pharmacological approach to manage their migraine. This constitute selection bias and, thus, this sample do not represent the general migraine population. Furthermore, this is a secondary, per-protocol analysis, which means that the analyses were designed after randomization. The strengths of this study lie on the trigger data collected through paper-based diary throughout the study period, and a supervised exercise program design.

Taking into account multiple neurophysiological and biochemical processes affected by physical exercise, and possible relation to migraine triggers mechanisms, further studies are needed to elucidate particular clinical responses of aerobic exercise training in a more representative sample.

CONCLUSIONS

The preventive effect of regular aerobic exercise may reflect on the triggers pattern of patients. Mostly by reducing the number of triggers, and the more frequent ones. Tracking the patient triggers profile during exercise training interventions may unravel specific clinical data, and further advance the understanding of the relationship between exercise and migraine. The implications on exercise prescription should be further explored in the future.

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